

WO9527061

Publication Title:

PROTEIN TYROSINE KINASE AGONIST ANTIBODIES

Abstract:

Abstract of WO9527061

Agonist antibodies are disclosed which bind to the extracellular domain of receptor protein tyrosine kinases pTKs, and thereby cause dimerization and activation of the intracellular tyrosine kinase domain thereof. The antibodies are useful for activating their respective receptor and thereby enabling the role of the tyrosine kinase receptor in cell growth and/or differentiation to be studied. Chimeric proteins comprising the extracellular domain of the receptor pTKs and an immunoglobulin constant domain sequence are also disclosed. Data supplied from the esp@cenet database - Worldwide

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C12N 15/12, C07K 16/28, 19/00, C12N 5/10, 15/85, A61K 39/395	A1	(11) International Publication Number: WO 95/27061 (43) International Publication Date: 12 October 1995 (12.10.95)
(21) International Application Number: PCT/US95/04228 (22) International Filing Date: 4 April 1995 (04.04.95) (30) Priority Data: 08/222,616 4 April 1994 (04.04.94) US (60) Parent Application or Grant (63) Related by Continuation US 08/222,616 (CIP) Filed on 4 April 1994 (04.04.94) (71) Applicant (for all designated States except US): GENENTECH, INC. [US/US]; 460 Point San Bruno Boulevard, South San Francisco, CA 94080-4990 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): BENNETT, Brian, D. [US/US]; 1332 Oddstad Boulevard, Pacifica, CA 94044 (US). GOEDEL, David [US/US]; 2115 Forestview Avenue, Hillsborough, CA 94010 (US). LEE, James, M. [US/US]; 705 Shelter Creek, San Bruno, CA 94066 (US). MATTHEWS, William [GB/US]; 560 Summit Springs Road, Woodside, CA 94062 (US). TSAI, Siao, Ping [-/US]; 519 Orange Avenue, South San Francisco, CA 94080 (US).	(74) Agents: LEE, Wendy, M. et al.; Genentech, Inc., 460 Point San Bruno Boulevard, South San Francisco, CA 94080-4990 (US). (81) Designated States: CA, JP, MX, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
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PROTEIN TYROSINE KINASE AGONIST ANTIBODIES

BACKGROUND OF THE INVENTIONFIELD OF THE INVENTION

The present invention relates to novel protein tyrosine kinase (pTK) genes, the proteins encoded by these genes, RNA nucleic acid sequences which hybridize to the genes, antibodies specific for the encoded proteins, chimeras of the proteins and methods of use therefor.

In particular, this application relates to agonist antibodies which are able to activate the tyrosine kinase domain of the receptor pTKs disclosed herein and pTK-immunoglobulin chimeras.

DESCRIPTION OF RELATED ART

Transduction of signals that regulate cell growth and differentiation is regulated in part by phosphorylation of various cellular proteins. Protein tyrosine kinases are enzymes that catalyze this process. Moreover, many act as growth factor receptors. The c-kit subgroup of receptor tyrosine kinases catalyze the phosphorylation of exogenous substrates, as well as tyrosine residues within their own polypeptide chains (Ullrich et al., Cell 61:203 [1990]). Members of the c-kit subgroup include FLT/FLK (Fetal Liver Kinase), FGF (Fibroblast Growth Factor Receptor) and NGF (Nerve Growth Factor Receptor).

The EPH tyrosine kinase subfamily, Eph, Elk, Eck, Eek, Hek, Hek2, Sek, Ehk-1, Ehk-2, Cek-4 to -10, Tyro 1, 4, 5 and 6, appears to be the largest subfamily of transmembrane tyrosine kinases (Hirai et al., Science 238:1717-1720 [1987]; Letwin et al., Oncogene 3:621-678 [1988]; Lhotak et al., Mol. Cell. Biol. 13:7071-7079 [1993]; Lindberg et al., Mol. Cell. Biol. 10:6316-6324 [1990]; Bohme et al., Oncogene 8:2857-2862 [1993]; and Wicks et al., Proc. Natl. Acad. Sci. USA 89:1611-1615 [1992]; Pasquale et al., Cell Regulation 2:523-534 [1991]; Sajjadi et al., New Biol. 3:769-778 [1991]; Wicks et al., Proc. Natl. Acad. Sci. USA 89:1611-1615 [1992]; Lhotak et al., Mol. Cell. Bio. 11:2496-2502 [1991]; Gilardi-Hebenstreit et al., Oncogene 7:2499-2506 [1992]; Lai et al., Neuron 6:691-704 [1991]; Sajjadi et al., Oncogene 8:1807-1813 [1993]; and Maisonnier et al., Oncogene 8:3277-3288 [1993]).

Additional pTKs and agonist antibodies thereto are needed in order to further study growth and differentiation of cells, for use as therapeutic agents and for diagnostic purposes. Accordingly, it is an

object of the present invention to provide novel pTK genes, the proteins encoded thereby, antibodies specific for the encoded proteins, chimeras of the proteins and methods of use thereof.

SUMMARY OF THE INVENTION

5 The genes isolated as described herein are referred to, collectively, as "protein tyrosine kinase genes" or "pTK genes". The nucleic acid sequences of some of these genes, isolated as discussed herein, show significant homology with previously identified protein tyrosine kinases containing extracellular domains, which function as growth factor receptors
10 (e.g., pTKs of the c-kit subgroup). Some of the pTK genes have been shown to be present in both megakaryocytic and lymphocytic cells.

 In particular, fourteen pTK genes have been identified. Two pTK genes, referred to as SAL-S1 and SAL-D4 were identified in megakaryocytic cells. SAL-D4 is related to the CSK family of intracellular pTKs and SAL-S1
15 is related to the FGF receptor family of pTKs. Five pTK genes, referred to as LpTKs, were identified in lymphocytic cells and have been shown to be present in megakaryocytes as well. One pTK gene, referred to as HpTK5, was identified in human hepatoma cells. Six pTK genes, referred to as bpTK genes, were found in human brain tissue.

20 The pTK genes, which are the subject of the present invention, were generally identified using two sets of degenerative oligonucleotide primers: a first set which amplifies all pTK DNA segments (SEQ ID NOS: 1-2), and a second set which amplifies highly conserved sequences present in the catalytic domain of the c-kit subgroup of pTKs (SEQ ID NOS: 3-4). The
25 pTK genes identified in this manner are described below.

 SAL-S1 is expressed in several megakaryocytic cell lines, but not in erythroid cell lines. The nucleotide sequence of part of SAL-S1 was obtained, revealing a sequence containing 160 base pairs (SEQ ID NO: 5). This isolated DNA fragment encoded an amino acid sequence (SEQ ID NO: 6)
30 which exhibited significant sequence homology with known protein tyrosine kinases of the FLT/FLK family. The deduced amino acid sequence of SAL-S1 (SEQ ID NO: 32) contains 1298 residues.

 SAL-D4, also expressed in megakaryocytic cells, is a DNA fragment containing the nucleotide sequence of 147 base pairs. (SEQ ID NO: 7). This
35 isolated DNA fragment encoded an amino acid sequence (SEQ ID NO: 8) which exhibited significant sequence homology with known protein tyrosine kinases of the CSK intracellular pTK family.

The LpTKs, including LpTK 2, LpTK 3, LpTK 4, LpTK 13 and LpTK 25, are expressed in lymphocytic cells, as well as megakaryocytic cells. The nucleotide sequence (151 base pairs) of the LpTK 3 gene was obtained (SEQ ID NO: 11). The nucleotide sequences of the LpTK 2, LpTK 4, and LpTK 13 genes contained 149 base pairs (SEQ ID NO: 9), 137 base pairs (SEQ ID NO: 13), and 211 base pairs (SEQ ID NO: 15) respectively. LpTK 25 has a nucleotide sequence of 3120 b.p. (SEQ ID NO: 22). A full length gene sequence has been obtained for LpTK 2 (SEQ ID NO: 19) which contains 7607 b.p. Additional sequencing of LpTK 4 revealed a sequence of 404 b.p. (SEQ ID NO: 21).

The HpTK5 gene, expressed in human hepatoma cells, has a nucleotide sequence of 3969 b.p. (SEQ ID NO: 23).

Nucleotide sequences of the bpTKs, including bpTK 1, bpTK 2, bpTK 3, bpTK 4, bpTK 5 and bpTK 7, are expressed in human brain tissue and encode proteins having the amino acid sequences of SEQ ID NOS: 25-29 and 34 respectively.

Thus, the present invention includes DNA isolated from a human megakaryocytic cell line, which hybridizes to DNA encoding an amino acid sequence which is highly conserved in the catalytic domain of protein tyrosine kinases of the c-kit subgroup.

The present invention also includes the proteins encoded by the pTK genes identified as described herein, which exhibit significant sequence homology with members of the c-kit subgroup of pTKs as well as the proteins encoded by HpTK5 and the bpTKs. The present invention also includes SAL-S1, SAL-D4, LpTK, HpTK5 and bpTK homologues or equivalents (i.e., proteins which have amino acid sequences substantially similar, but not identical, to that of SAL-S1, SAL-D4, the LpTKs, HpTK5 and the bpTKs, which exhibit tyrosine kinase activity). This invention further includes peptides (SAL-S1, SAL-D4, LpTK, HpTK5 and bpTK fragments) which retain tyrosine kinase activity, yet are less than the entire SAL-S1, SAL-D4, LpTK, HpTK5 and bpTK sequences; and uses for the SAL-S1, SAL-D4, the LpTK, HpTK and the bpTK nucleic acid sequences and SAL-S1, SAL-D4, LpTK, HpTK and bpTK equivalents.

The present invention further includes nucleic acid sequences which hybridize with DNA or RNA encoding the proteins described herein, which exhibit significant sequence homology with the FLT/FLK, FGF receptor or NGF receptor family of protein tyrosine kinases contained within the c-kit subgroup. Such nucleic acid sequences are useful as probes to identify pTK genes in other vertebrates, particularly mammals, and in other cell types.

They can also be used as anti-sense oligonucleotides to inhibit protein tyrosine kinase activity, both in vitro and in vivo.

The SAL-S1, SAL-D4, LpTK, HpTK and bpTK tyrosine kinases of the present invention can be used as target proteins in conjunction with the development of drugs and therapeutics to modulate cell growth, differentiation and other metabolic functions. The SAL-S1, SAL-D4, LpTK, HpTK or bpTK proteins can be used as agonists or antagonists to other tyrosine kinases. The pTKs can also be instrumental in the modulation of megakaryocyte and/or platelet adhesion interactions.

10 In addition, the SAL-S1, SAL-D4, LpTK, HpTK and bpTK tyrosine kinases can be used in screening assays to detect cellular growth and/or differentiation factors. Using standard laboratory techniques, the ligands of the pTKs of the present invention can be identified. In particular, the invention provides chimeric pTK-immunoglobulin fusion proteins which are
15 useful for isolating ligands to the pTKs disclosed herein. The chimeric proteins are also useful for diagnostic assays designed to detect these ligands present endogenously, within cells, as well as exogenously, in extra-cellular fluids. Assays, using the chimeric proteins, can also be designed as diagnostic aids to detect these ligands in body fluids such as
20 blood and urine.

In another aspect, the invention provides antibodies specific for SAL-S1, SAL-D4, the LpTKs, HpTK5 and the bpTKs, which are optionally agonists for their respective pTK (where the pTK is a receptor). The invention also concerns a hybridoma cell line and an isolated nucleic acid
25 encoding a monoclonal antibody as herein defined.

Also, the invention pertains to a method for activating a pTK as herein disclosed, comprising reacting the pTK with an agonist antibody thereto. In a different aspect, the invention concerns a method for enhancing cell growth and/or differentiation comprising administering to
30 a human patient in need of such treatment a physiologically effective amount of an agonist antibody which activates a pTK as herein disclosed.

In a still further aspect, the invention concerns a method for detecting a pTK by contacting a source suspected of containing the pTK with a detectably labeled monoclonal antibody which reacts immunologically with
35 the pTK, and determining whether the antibody binds to the source.

BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1A and 1B depict the nucleotide sequence of SAL-S1 (SEQ ID NO: 5) and its deduced amino acid sequence (SEQ ID NO: 6).

Figures 2A and 2B depict the nucleotide sequence of SAL-D4 (SEQ ID NO: 7) and its deduced amino acid sequence (SEQ ID NO: 8).

Figure 3A depicts the nucleotide sequence of LpTK 2 (SEQ ID NO: 9) and its deduced amino acid sequence (SEQ ID NO: 10).

Figure 3B depicts the nucleotide sequence of LpTK 3 (SEQ ID NO: 11) and its deduced amino acid sequence (SEQ ID NO: 12).

Figure 3C depicts the nucleotide sequence of LpTK 4 (SEQ ID NO: 13) and its deduced amino acid sequence (SEQ ID NO: 14).

Figure 3D depicts the nucleotide sequence of LpTK 13 (SEQ ID NO: 15) and its deduced amino acid sequence (SEQ ID NO: 16).

Figures 4A-4I depict the nucleotide sequence (SEQ ID NO: 17) of SAL-S1 and its deduced amino acid sequence (SEQ ID NO: 18).

Figures 5A-5K depict the full length nucleotide sequence (SEQ ID NO: 19) of LpTK2 and its deduced amino acid sequence (SEQ ID NO: 20).

Figure 6 depicts the partial nucleotide sequence (SEQ ID NO: 21) for LpTK4.

Figures 7A-7C depict the full length nucleotide sequence (SEQ ID NO: 22) for LpTK25.

Figures 8A-8I depict the full length nucleotide sequence (SEQ ID NO: 23) and the deduced amino acid sequence of HpTK5 (SEQ ID NO: 24).

Figure 9 depicts the amino acid sequence (SEQ ID NO: 25) of bpTK1.

Figure 10 depicts the amino acid sequence (SEQ ID NO: 26) of bpTK2.

Figure 11 depicts the amino acid sequence (SEQ ID NO: 27) of bpTK3.

Figure 12 depicts the amino acid sequence (SEQ ID NO: 28) of bpTK4.

Figure 13 depicts the amino acid sequence (SEQ ID NO: 29) of bpTK5.

Figure 14 depicts the amino acid sequence (SEQ ID NO: 30) of bpTK7.

Figures 15A-15F depict the full-length nucleotide sequence of SAL-S1 (SEQ ID NO: 31) and its deduced amino acid sequence (SEQ ID NO: 32).

Figures 16A-16H depict the full-length nucleotide sequence of bpTK7 (SEQ ID NO: 33) and its deduced amino acid sequence (SEQ ID NO: 34).

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Novel protein tyrosine kinase genes have been identified, their nucleic acid sequences determined, and the amino acid sequences of the encoded proteins deduced. The genes isolated as described herein are

referred to, collectively, as "protein tyrosine kinase genes" or "pTK genes".

To facilitate the isolation and identification of these novel pTKs, two sets of DNA probes were used, as described in Example 1. The first set
5 generally consisted of two degenerative oligonucleotide sequences, pTK 1 (SEQ ID NO: 1) and pTK 2 (SEQ ID NO: 2) (Matthews, Cell 65:1143 [1991]; and Wilks, Proc. Natl. Acad. Sci. USA 86:1603 [1989]). These sequences were used as primers in a polymerase chain reaction to amplify tyrosine kinase DNA segments (Mullis, et al., Cold Spring Harbor Symp. Advan. Biol. 51:263
10 [1986]).

The second set generally consisted of two oligonucleotide sequences, pTK 3 (SEQ ID NO: 3) and pTKKW (SEQ ID NO: 4) designed to amplify the nucleic acid sequence which encodes the highly conserved regions of the catalytic domains of the c-kit family of protein tyrosine kinases. These
15 sequences were used as primers in the polymerase chain reaction (PCR) in a second round of DNA amplification. Using this two-step amplification procedure, DNA fragments which hybridized to these pTK primers were identified, isolated and subsequently sequenced.

In particular, fourteen pTK genes have been identified. Two pTK
20 genes, referred to as SAL-S1 and SAL-D4, were identified in several megakaryocytic cell lines, including CMK 11-5, DAMI, UT-7 and UT-7 grown in erythropoietin, but not in the erythroid cell lines HEL, PMA stimulated HEL cells, or K562. Five pTK genes, referred to as LpTKs, were identified in lymphocytic, as well as in megakaryocytic cells. One pTK gene, referred
25 to as HpTK5, was identified in human hepatoma cells, and six genes, referred to as bpTKs, were identified in human brain tissue.

SAL-S1 (SEQ ID NOS: 6, 18 and 32) encoded by the nucleic acid sequence of SEQ ID NOS: 5, 17 and 31 exhibits significant homology with the FLT/FLK family of pTKs. SAL-S1 has a signal peptide (i.e., amino acid
30 residues 1 to 24 of Figure 15); extracellular domain (i.e., amino acid residues 25 to 775 of Figure 15); transmembrane domain (i.e., amino acid residues 776 to 800 of Figure 15) and a cytoplasmic tyrosine kinase domain (i.e., amino acid residues 801 to 1298 of Figure 15). SAL-D4 (SEQ ID NO: 8) encoded by SEQ ID NO: 7 is related to the CSK family of intracellular
35 pTKs. The LpTKs, LpTK 2 (SEQ ID NOS: 10 and 20) encoded by SEQ ID NOS: 9 and 19; LpTK 3 (SEQ ID NO: 12) encoded by SEQ ID NO: 11; LpTK4 (SEQ ID NO: 14) encoded by SEQ ID NOS: 13 and 21; LpTK13 (SEQ ID NO: 16) encoded by SEQ

ID NO: 15; and LpTK25 encoded by SEQ ID NO: 22, also exhibit sequence homology with known protein tyrosine kinases.

HpTK5 (SEQ ID NO: 24) encoded by SEQ ID NO: 23 and the bpTKs 1, 2, 3, 4, 5 and 7 (SEQ ID NOS: 25-29 and 34 respectively), similarly exhibit sequence homology with known protein tyrosine kinases. BpTK7 encodes a receptor pTK with a signal peptide (i.e., amino acid residues 1-19 of Figure 16); extracellular domain (i.e., amino acid residues 20-547 of Figure 16); and transmembrane domain (i.e., amino acid residues 548-570 of Figure 16). The remaining sequence comprises the intracellular tyrosine kinase domain.

Thus, as described above, DNA molecules which hybridize with DNA encoding amino acid sequences present in the catalytic domain of a protein tyrosine kinase of the c-kit subgroup of protein kinases have been isolated and sequenced. These isolated DNA sequences, collectively referred to as "pTK genes", (and their deduced amino acid sequences) have been shown to exhibit significant sequence homology with known members of pTK families.

Once isolated, these DNA fragments can be amplified using known standard techniques such as PCR. These amplified fragments can then be cloned into appropriate cloning vectors and their DNA sequences determined.

These DNA sequences can be excised from the cloning vectors, labeled with a radiolabeled nucleotide such as ³²P and used to screen appropriate cDNA libraries to obtain the full-length cDNA clone.

The pTK genes as described above have been isolated from the source in which they occur naturally, e.g., megakaryocytic and lymphocytic cells. The present invention is intended to include pTK genes produced using genetic engineering techniques, such as recombinant technology, as well as pTK genes that are synthesized chemically.

The deduced amino acid sequences of the pTK genes include amino acid sequences which encode peptides exhibiting significant homology with the catalytic domain of protein tyrosine kinases of the c-kit subgroup of tyrosine kinases. These proteins, encoded by the pTK genes, can include sequences in which functionally equivalent amino acid residues are substituted for residues within the sequence, resulting in a silent change, that is a change not detected phenotypically. For example, one or more amino acid residues within the sequence can be substituted by another amino acid of a similar polarity which acts as a functional equivalent, resulting in a silent substitution.

In addition, the protein structure can be modified by deletions, additions, inversion, insertions or substitutions of one or more amino acid residues in the sequence which do not substantially detract from the desired functional tyrosine kinase properties of the peptide.

5 Modified pTKs of the present invention, with tyrosine kinase activity, can be made using recombinant DNA techniques, such as excising it from a vector containing a cDNA encoding such a protein, or by synthesizing DNA encoding the desired protein mechanically and/or chemically using known techniques.

10 An alternate approach to producing the pTKs of the present invention is to use peptide synthesis to make a peptide or polypeptide having the amino acid sequence of such a protein, depending on the length of the pTK desired. The peptides or modified equivalents thereof, can be synthesized directly by standard solid or liquid phase chemistries for peptide
15 synthesis.

Preferably, the pTKs of the present invention will be produced by inserting DNA encoding the proteins into an appropriate vector/host system where it will be expressed. The DNA sequences can be obtained from sources in which they occur naturally, can be chemically synthesized or can be
20 produced using standard recombinant technology.

This invention also pertains to an expression vector comprising a pTK gene of the present invention, encoding for a protein which exhibits receptor tyrosine kinase activity.

The pTK genes of the present invention can be used for a number of
25 diagnostic and therapeutic purposes. For example, the nucleic acid sequences of the pTK genes can be used as probes to identify other protein tyrosine kinases present in other cell types, including eukaryotic and prokaryotic cell types.

The nucleic acid sequences can also be used to design drugs that
30 directly inhibit the kinase activity of protein tyrosine kinases, or to design peptides that bind to the catalytic domain of tyrosine kinases, thus inhibiting their activity. These sequences can also be used to design anti-sense nucleotides that can also inhibit, or destroy, tyrosine kinase activity. Such inhibition of tyrosine kinase activity would be desirable
35 in pathological states where decreased cellular proliferation would be beneficial, such as leukemias or other malignancies.

The nucleic acid sequences can also be used to design drugs, peptides or anti-sense nucleotides as above, but with enhancing, rather than

inhibitory effects, on tyrosine kinases. Such enhanced tyrosine kinase activity would result in increasing the phosphorylation of substrates (exogenous, as well as endogenous tyrosine residues). Enhanced effects would be desirable in states where increased cellular proliferation would be beneficial, such as anemias, bleeding disorders and during surgical procedures.

The pTK genes of the present invention can also be used to obtain soluble fragments of receptor tyrosine kinases, capable of binding their respective ligands. pTK genes encoding soluble tyrosine kinase fragments can be produced using recombinant DNA techniques or synthetically. In either case, the DNA obtained encodes a soluble pTK fragment which lacks a substantial portion of the hydrophobic transmembrane region to permit solubilization of the fragment.

These soluble pTK protein fragments can be introduced exogenously to act as competitors with the endogenous, membrane bound pTK for their respective ligands, thus inhibiting tyrosine kinase activity. Alternately, a modified soluble pTK protein fragment can be introduced which binds the ligand but does not activate kinase activity.

These soluble pTK protein fragments can also be used in binding assays to detect ligands such as growth and differentiation factors. Once these ligands are identified, they may be altered or modified to inhibit or enhance kinase activity. For example, the ligands may be modified or attached to substances that are toxic to the cell, such a ricin, thus destroying the target cell. The substance may be a super-activating substance which, after binding to the pTK, may substantially increase the kinase activity, or activate other growth factors.

pTK genes of the present invention would also be useful to develop diagnostic tools for *in vitro* screening assays for ligands such as growth factors or differentiation factors that inhibit or enhance kinase activity. The proteins encoded by the pTK genes can also be used in such assays, or as immunogens to produce monoclonal or polyclonal antibodies to be used in such assays.

In one embodiment of the invention, a chimera comprising a fusion of the extracellular domain of the pTK (where the pTK is a receptor) and an immunoglobulin constant domain can be constructed which can be used to assay for ligands for the receptor and can be used for the production of antibodies against the extracellular domain of the receptor.

The expression "extracellular domain" or "ECD" when used herein refers to any polypeptide sequence that shares a ligand binding function of the extracellular domain of the naturally occurring receptor pTKs disclosed herein. Ligand binding function of the extracellular domain refers to the ability of the polypeptide to bind at least one pTK ligand. Accordingly, it is not necessary to include the entire extracellular domain since smaller segments are commonly found to be adequate for ligand binding. The truncated extracellular domain is generally soluble. The term ECD encompasses polypeptide sequences in which the hydrophobic transmembrane sequence (and, optionally, 1-20 amino acids C-terminal and/or N-terminal to the transmembrane domain) of the mature pTK has been deleted. Thus, the soluble extracellular domain-containing polypeptide can comprise the extracellular domain and the cytoplasmic domain of the pTK. Alternatively, in the preferred embodiment, the polypeptide comprises only the extracellular domain of the pTK. The extracellular and transmembrane domains of the pTK can be readily determined by the skilled practitioner by aligning the pTK of interest with known pTK amino acid sequences for which these domains have been delineated. Alternatively, the hydrophobic transmembrane domain can be readily delineated based on a hydrophobicity plot of the sequence. The extracellular domain is N-terminal to the transmembrane domain.

The term "immunoglobulin" generally refers to polypeptides comprising a light or heavy chain usually both disulfide bonded in the native "Y" configuration, although other linkage between them, including tetramers or aggregates thereof, is within the scope hereof.

Immunoglobulins (Ig) and certain variants thereof are known and many have been prepared in recombinant cell culture. For example, see U.S. Patent 4,745,055; EP 256,654; Faulkner et al., Nature 298:286 [1982]; EP 120,694; EP 125,023; Morrison, J. Immun. 123:793 [1979]; Köhler et al., Proc. Nat'l. Acad. Sci. USA 77:2197 [1980]; Raso et al., Cancer Res. 41:2073 [1981]; Morrison et al., Ann. Rev. Immunol. 2:239 [1984]; Morrison, Science 229:1202 [1985]; Morrison et al., Proc. Nat'l. Acad. Sci. USA 81:6851 [1984]; EP 255,694; EP 266,663; and WO 88/03559. Reassorted immunoglobulin chains also are known. See for example U.S. patent 4,444,878; WO 88/03565; and EP 68,763 and references cited therein. The immunoglobulin moiety in the chimera of the present invention may be obtained from IgG₁, IgG₂, IgG₃, or IgG₄ subtypes, IgA, IgE, IgD or IgM, but

preferably IgG₁ or IgG₃. Most preferably, the immunoglobulin moiety is the Fc portion of IgG-γ.

The terms "chimera comprising a fusion of an extracellular domain of a pTK with an immunoglobulin constant domain sequence" or "pTK-immunoglobulin chimera" refer to a polypeptide comprising an extracellular domain coding amino acid sequence of a pTK conjugated to an immunoglobulin constant domain sequence. This definition includes chimeras in monomeric, homo- or heteromultimeric, and particularly homo- or heterodimeric, or tetrameric forms.

10 A preferred embodiment is the fusion of the C-terminus of the extracellular domain of a pTK, to the N-terminus of the C-terminal portion of an antibody (in particular the Fc domain), containing the effector functions of immunoglobulin G₁. In a preferred embodiment, the entire heavy chain constant region is fused to the extracellular domain. In another
15 preferred embodiment, a sequence beginning in the hinge region just upstream of the papain cleavage site (which defines IgG Fc chemically; residue 216, taking the first residue of heavy chain constant region to be 114 (Kabat et al., Sequences of Immunological Interest, National Institutes of Health, Bethesda, MD, [1987]), or analogous sites of other
20 immunoglobulins) is fused to the ECD of the pTK.

In a particularly preferred embodiment, the pTK extracellular domain is fused to the hinge region and C_H2 and C_H3 or C_H1, hinge, C_H2 and C_H3 domains of an IgG₁, IgG₂, or IgG₃ heavy chain. The precise site at which the fusion is made is not critical, and the optimal site can be determined by
25 routine experimentation. A principal advantage of the chimeras is that they are secreted into the culture medium of recombinant hosts, although the degree of secretion might be different for various expression systems.

In general, the chimeras of the present invention are constructed in a fashion similar to chimeric antibodies in which a variable domain from
30 an antibody of one species is substituted for the variable domain of another species. See, for example, EP 0 125 023; EP 173,494; Munro, Nature 312: [13 December 1984]; Neuberger et al., Nature 312: [13 December 1984]; Sharon et al., Nature 309: [24 May 1984]; Morrison et al., Proc. Nat'l. Acad. Sci. USA 81:6851-6855 [1984]; Morrison et al. Science 229:1202-1207
35 [1985]; Boulianne et al., Nature 312:643-646 [13 December 1984]; Capon et al., Nature 337, 525-531 [1989]; Traunecker et al., Nature 339, 68-70 [1989].

To prepare the pTK-Ig chimeric polypeptides, the DNA including a region encoding the desired pTK sequence is cleaved by a restriction enzyme at or proximal to the 3' end of the DNA encoding the immunoglobulin-like domain(s) and at a point at or near the DNA encoding the N-terminal end of the mature pTK (where use of a different leader is contemplated) or at or proximal to the N-terminal coding region for the pTK (where the native signal is employed). This DNA fragment then is readily inserted proximal to DNA encoding an immunoglobulin light or heavy chain constant region and, if necessary, the resulting construct tailored by deletional mutagenesis.

10 Preferably, the Ig is a human immunoglobulin when the variant is intended for in vivo therapy for humans. DNA encoding immunoglobulin light or heavy chain constant regions is known or readily available from cDNA libraries or is synthesized. See for example, Adams et al., Biochemistry 19:2711-2719 [1980]; Gough et al., Biochemistry 19:2702-2710 [1980]; Dolby et al., P.N.A.S. USA, 77:6027-6031 [1980]; Rice et al., P.N.A.S. USA 79:7862-7865 [1982]; Falkner et al., Nature 298:286-288 [1982]; and Morrison et al., Ann. Rev. Immunol. 2:239-256 [1984].

The chimeric proteins disclosed herein are useful as diagnostics for isolating or screening ligands for the pTK of interest using the techniques of Lyman et al., Cell 75:1157-1167 [1993], for example. Also, the chimeric proteins are useful for diagnostic purposes for studying the interaction of various ligands with the extracellular domain of the various pTKs (see, e.g., Bennett et al., J. Biol. Chem. 266(34):23060-23067 [1991]). The chimeric proteins are further useful for the production of antibodies

25 against the extracellular domain of the pTK (see Examples 3 and 5 herein). The chimeric proteins also have an additional therapeutic utility insofar as they provide a soluble form of the extracellular domain of the pTK which generally has an enhanced plasma half life (compared to the extracellular domain only) and therefore can be formulated in a pharmaceutically acceptable carrier and administered to a patient. The chimeric proteins are believed to find use as therapeutic agents for removal of excess systemic or tissue-localized pTK ligand which has been administered to a patient. Removal of excess ligand is particularly desirable where the ligand may be toxic to the patient. The chimeric protein acts to bind the ligand in

30 competition with the endogenous pTK in the patient. Similarly, it is contemplated that the chimeric protein can be administered to a patient simultaneously, or subsequent to, administration of the ligand in the form of a sustained release composition. The chimeric protein acts as a soluble

binding protein for the ligand, thereby extending the half-life of the ligand.

The term "antibody" is used herein in the broadest sense and specifically covers polyclonal antibodies, monoclonal antibodies, immunoglobulin chains or fragments thereof, which react immunologically with a pTK.

In the preferred embodiment of the invention, the antibodies are monoclonal antibodies produced using techniques which are well known in the art. For example, the hybridoma technique described originally by Kohler and Milstein, Eur. J. Immunol., 5:511 [1976], and also described by Hammerling et al., In: Monoclonal Antibodies and T-Cell Hybridomas, Elsevier, N.Y., pp. 563-681 [1981] can be used. The techniques of Cote et al. and Boerner et al. are also available for the preparation of human monoclonal antibodies [Cote et al., Monoclonal Antibodies and Cancer Therapy, Alan R. Liss, p. 77 [1985] and Boerner et al., J. Immunol., 147(1):86-95 [1991]].

The term "monoclonal antibody" as used herein refers to an antibody (as hereinabove defined) obtained from a population of substantially homogeneous antibodies, i.e., the individual antibodies comprising the population are identical except for possible naturally occurring mutations that may be present in minor amounts. Monoclonal antibodies are highly specific, being directed against a single antigenic site. Furthermore, in contrast to conventional (polyclonal) antibody preparations which typically include different antibodies directed against different determinants (epitopes), each monoclonal antibody is directed against a single determinant on the antigen. In addition to their specificity, the monoclonal antibodies are advantageous in that they can be synthesized by a hybridoma culture, uncontaminated by other immunoglobulins.

"Humanized" forms of non-human (e.g., murine) antibodies are immunoglobulins, immunoglobulin chains or fragments thereof (such as Fv, Fab, Fab', F(ab')), or other antigen-binding subsequences of antibodies) which contain minimal amino acid residues derived from a non-human immunoglobulin. For the most part, humanized antibodies are human immunoglobulins (recipient antibody) in which residues from a complementary determining region (CDR) of the recipient are replaced by residues from a CDR of a non-human species (donor antibody) such as mouse, rat or rabbit having the desired specificity, affinity and capacity. In some instances, Fv framework region (FR) residues of the human immunoglobulin are replaced

by corresponding non-human FR residues. Furthermore, a humanized antibody may comprise residues which are found neither in the recipient antibody nor in the imported CDR or framework sequences. These modifications are made to further refine and optimize antibody performance.

5 The monoclonal antibodies herein include hybrid (chimeric) and recombinant antibodies produced by splicing a variable (including hypervariable) domain of an anti-pTK antibody with a constant domain (e.g., "humanized" antibodies), only one of which is directed against a pTK, or a light chain with a heavy chain, or a chain from one species with a chain
10 from another species, or fusions with heterologous proteins, regardless of species of origin or immunoglobulin class or subclass designation, so long as they are able to bind to the pTK of interest [See, e.g., Cabilly, et al., U.S. Patent No. 4,816,567; and Mage & Lamoyi, in Monoclonal Antibody Production Techniques and Applications, pp.79-97 (Marcel Dekker, Inc., New
15 York [1987])].

For "chimeric" and "humanized" antibodies see, for example, U.S. Patent No. 4,816,567; WO 91/09968; EP 452,508; and WO 91/16927.

Thus, the modifier "monoclonal" indicates the character of the antibody as being obtained from a substantially homogeneous population of
20 antibodies, and is not to be construed as requiring production of the antibody by any particular method.

In the most preferred embodiment of the invention, the antibodies are agonist antibodies. By "agonist antibody" is meant an antibody which is able to bind to, and activate, a particular pTK. For example, the agonist
25 may bind to the extracellular domain of the pTK and thereby cause dimerization of the pTK, resulting in transphosphorylation and activation of the intracellular catalytic kinase domain. Consequently, this may result in stimulation of growth and/or differentiation of cells expressing the receptor *in vitro* and/or *in vivo*. The agonist antibodies herein are
30 preferably against epitopes within the extracellular domain of the pTK, and preferably have the same biological characteristics as the monoclonal antibody produced by the hybridoma cell line deposited under American Type Culture Collection Accession No. ATCC HB 11,583. By "biological characteristics" is meant the *in vitro* and/or *in vivo* activities of the
35 monoclonal antibody, e.g., ability to activate the kinase domain of a particular pTK, ability to stimulate cell growth and/or differentiation of cells expressing the pTK, and binding characteristics of the antibody, etc. Accordingly, the antibody preferably binds to substantially the same

epitope as the anti-HpTK5 monoclonal antibody specifically disclosed herein. Most preferably, the antibody will also have substantially the same or greater antigen binding affinity of the anti-HpTK5 monoclonal antibody disclosed herein. To determine whether a monoclonal antibody has
5 the same specificity as the anti-HpTK5 antibody specifically disclosed (i.e., the antibody having the ATCC deposit No. HB 11,583), one can, for example, use a competitive ELISA binding assay.

DNA encoding the monoclonal antibodies useful in the method of the invention is readily isolated and sequenced using conventional procedures
10 (e.g., by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of murine antibodies). The hybridoma cells of the invention serve as a preferred source of such DNA. Once isolated, the DNA may be placed into expression vectors, which are then transfected into host cells such as E. coli cells,
15 simian COS cells, Chinese Hamster Ovary (CHO) cells, or myeloma cells that do not otherwise produce immunoglobulin protein, to obtain the synthesis of monoclonal antibodies in the recombinant host cells.

The agonist antibodies disclosed herein are useful for in vitro diagnostic assays for activating the pTK receptor of interest. This is
20 useful in order to study the role of the receptor in cell growth and/or differentiation.

The pTK agonist antibodies have a further therapeutic utility in a method for enhancing cell growth and/or differentiation comprising administering to a human patient in need of such treatment a
25 physiologically effective amount of an exogenous pTK agonist antibody. Agonist antibodies to the SAL-S1 pTK may find utility in treating bleeding disorders and anemias, since this pTK was found to be expressed in megakaryocytic cells. The bpTK agonist antibodies may similarly be used to enhance differentiation and/or proliferation of brain cells in
30 neurodegenerative diseases (such as Alzheimers disease) based on the expression of these receptors in brain tissue. Finally, HpTK5 agonist antibodies may be used to enhance proliferation of primitive hematopoietic cells in patients having undergone chemo- or radiation therapy or bone marrow transplantation.

35 An "exogenous" therapeutic compound is defined herein to mean a therapeutic compound that is foreign to the mammalian patient, or homologous to a compound found in the mammalian patient but produced outside the mammalian patient.

The antibodies of the present invention are also suitable for detecting a pTK by contacting a source suspected to contain the pTK with a detectably labeled monoclonal antibody, and determining whether the antibody binds to the source. There are many different labels and methods
5 of labeling known in the art. Suitable labels include, for example, enzymes, radioisotopes, fluorescent compounds, chemi- and bioluminescent compounds, paramagnetic isotopes. The pTK may be present in biological samples, such as biological fluids or tissues. For analytical or diagnostic purposes, the antibodies of the present invention are
10 administered in an amount sufficient to enable the detection of a site on a pTK for which the monoclonal antibody is specific. The concentration of the detectably labeled monoclonal antibody should be sufficient to give a detectable signal above background, when bound to a pTK epitope.

The pTK agonist antibodies disclosed herein may be administered to
15 a mammal, preferably a human, in a pharmaceutically acceptable dosage form, including those that may be administered to a human intravenously as a bolus or by continuous infusion over a period of time, by intramuscular, subcutaneous, intra-articular, intrasynovial, intrathecal, oral, topical, or inhalation routes.

20 Such dosage forms encompass pharmaceutically acceptable carriers that are inherently nontoxic and nontherapeutic. Examples of such carriers include ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride
25 mixtures of saturated vegetable fatty acids, water, salts, or electrolytes such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, and polyethylene glycol. Carriers for topical or gel-based forms of antibody
30 include polysaccharides such as sodium carboxymethylcellulose or methylcellulose, polyvinylpyrrolidone, polyacrylates, polyoxyethylene-polyoxypropylene-block polymers, polyethylene glycol, and wood wax alcohols. For all administrations, conventional depot forms are suitably used. Such forms include, for example, microcapsules, nano-capsules,
35 liposomes, plasters, inhalation forms, nose sprays, and sublingual tablets. The antibody will typically be formulated in such vehicles at a concentration of about 0.1 mg/ml to 100 mg/ml.

Pharmaceutical compositions may be prepared and formulated in dosage forms by methods known in the art; for example, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pennsylvania, 15th Edition 1975.

5 An effective amount of the pTK agonist antibody to be employed therapeutically will depend, for example, upon the therapeutic objectives, the route of administration, and the condition of the patient. Accordingly, it will be necessary for the therapist to titer the dosage and modify the route of administration as required to obtain the optimal
10 therapeutic effect. A typical daily dosage might range from about 1 μ g/kg to up to 1000 mg/kg or more, depending on the factors mentioned above. Typically, the clinician will administer the molecule until a dosage is reached that achieves the desired effect. The progress of this therapy is easily monitored by conventional assays.

15 Depending on the type and severity of the disease, from about 0.001 mg/kg to about 1000 mg/kg, more preferably about 0.01 mg to 100 mg/kg, more preferably about 0.010 to 20 mg/kg of the agonist antibody might be an initial candidate dosage for administration to the patient, whether, for example, by one or more separate administrations, or by continuous
20 infusion. For repeated administrations over several days or longer, depending on the condition, the treatment is repeated until a desired suppression of disease symptoms occurs or the desired improvement in the patient's condition is achieved. However, other dosage regimens may also be useful.

25 The present invention will now be illustrated by the following Examples, which are not intended to be limiting in any way. The disclosures of all literature references cited in the specification are expressly incorporated herein by reference.

EXAMPLE 1

IDENTIFICATION AND ISOLATION OF pTK GENES

30 To facilitate the isolation and identification of these novel pTK genes, two sets of DNA probes were generally used (see Table 1).

 The first set consisted of two degenerate oligonucleotide sequences, pTK 1 (SEQ ID NO: 1) and pTK 2 (SEQ ID NO: 2). These sequences were used
35 as polymerase chain reaction (PCR) primers, using standard PCR techniques, to amplify tyrosine kinase DNA segments.

The second set consisted of two oligonucleotide sequences, pTK 3 (SEQ ID NO: 3) and pTKKW (SEQ ID NO: 4) selected from the highly conserved regions of the catalytic domains of the c-kit subgroup of protein tyrosine kinases. These sequences were also used as polymerase chain reaction primers in a second round of DNA amplification. Using this two-step amplification procedure, DNA fragments which hybridized to these pTK primers were identified, isolated and subsequently sequenced using known laboratory techniques.

TABLE 1

<u>First Round of Amplification</u>	
<u>Probe name</u>	<u>Sequence</u>
pTK1	5'-CGGATCCACAGNGACCT-3'
pTK2	5'-GGAATTCCAAAGGACCAGACGTC-3'
<u>Second Round of Amplification</u>	
15 pTK3 (kit family specific)	5'-CGGATCCATCCACAGAGATGT-3'
pTKKW (kit family specific)	5'-GGAATTCCTTCAGGAGCCATCCACTT-3'

EXAMPLE 2ISOLATION AND CHARACTERIZATION OF HpTK5A. DNA Amplification and Cloning of HpTK5

20 Light density human bone marrow mononuclear cells, obtained from normal volunteers using Deaconess Hospital Institutional Review Board approved protocols and with voluntary written informed consent, were separated by anti-CD34 antibody (AMAC, Westbrook, ME) and immunomagnetic beads (Dynal, Oslo, Norway). Flow cytometric analysis using FITC-
 25 conjugated anti-CD34 antibody (AMAC) confirmed ~95% CD34 positivity of isolated cells. The hepatoma cell line, Hep3B, was cultured in alpha medium (Gibco, Grand Island, NY) supplemented with penicillin (100U/mL), streptomycin (100µg/mL) and 10% fetal bovine serum (Gibco) at 37°C in a 5% CO₂ incubator. Total RNA extracted from CD34+ bone marrow mononuclear
 30 or Hep3B cells was reverse transcribed with random primers and the Moloney murine leukemia virus reverse transcriptase (RT) following the conditions of the manufacturer (Gibco-BRL) in a 20 µl reaction. PCR was performed on the RT reaction product in a 100µl reaction containing 50mM KCl, 10mM Tris-HCl (pH 8.4), 1.5mM MgCl₂, 20 µg/ml gelatin, 0.2mM dNTPs,

2.5 units Taq polymerase (Perkin-Elmer/Cetus) and 50pmol each of pTK-specific degenerate primers

[pTK1 5'TCGGATCCACA/CGNGAC/TC/TTGGC 3' (SEQ ID NO. 35),

pTK1B 5'TCGGATCCAC/TC/AGNGAC/TC/TTNGCNGC 3' (SEQ ID NO. 36),

5 pTK2 5'CTCGAATTCCA/GA/TAA/GC/GT/ACCAG/CACA/GTC 3' (SEQ ID NO. 37),

pTK2B 5'CTCGAATTCCA/GA/TAT/CC/GT/ACCAT/AACA/GTC 3'(SEQ ID NO. 38)]

derived from consensus regions among known pTKs as previously reported by others (Hanks et al., Science, 241:42-52 [1988]; Wilks, Proc. Nat. Acad. Sci. USA 86:1603-1607 [1989]; and Matthews et al., Cell 65:1143-

10 1152 [1991]). The PCR cycle was 1.5min at 95°C, 2min at 37°C and 3 min at 63°C repeated 35 times. The reaction product was electrophoretically separated on a 2% low-melting agarose gel, purified on an Elutip-D column (Schleicher & Schuell) digested with EcoR1 and BamH1, and subcloned into pUC19.

15 Recombinants were sequenced by the Sanger dideoxy method and evaluated by the FASTA nucleic acid sequence analysis program. One clone termed HpTK5 (214 bp) was radiolabelled by random priming and used to screen an oligo dT-primed lambda gt10 Hep3B cDNA library. DNA was isolated from 17 positive phage plaques and inserts were subcloned into
20 the EcoR1 site of pBluescript (Stratagene La Jolla, CA). The largest insert, a 3969 bp cDNA, was sonicated to an average size of 800-2000 bp and cloned into the Sma1 site of M13. Overlapping clones were sequenced using the Taq Dye Primer Cycle Method (CABI) on the Catalyst 800 Molecular Biology Lab Station (ABI). Sequencing reactions were then
25 analyzed on the ABI 373A Automated DNA Sequenator.

A single full-length 3969 bp cDNA was isolated and sequenced. (Figures 8A-8F). The full length clone, named hepatoma transmembrane kinase (HTK) or HpTK5, included an open reading frame extending from nucleotide 90 to 3050 predicted to encode a 987 amino acid protein of
30 108,270 Dalton. The putative initiation codon is preceded by an in-frame stop codon beginning at base 78. Preceding the open reading frame is a 5' untranslated region which is GC-rich as is characteristic for many growth factors or growth factor receptors (Kozak, J. Cell Biol. 115:887-903 [1991]).

35 The predicted protein sequence includes a transmembrane region (aa 538-563) which divides HpTK5 into extracellular (ECD) and intracellular domains (ICD). The ECD of 538 amino acids includes a signal peptide of 15 amino acids and a cysteine-rich box containing 20 Cys residues. In

addition, there are two fibronectin type III repeats spanning aa 321 to 425 and 435 to 526. Asn at positions 208, 340 and 431 are possible sites for N-glycosylation.

The putative intracellular domain (ICD) contains a kinase consensus region from position 613 through 881. This kinase region includes a putative ATP-binding consensus (Gly-X-Gly-X-X-Gly) in subdomain I at positions 622-627. A Lys at position 647 (subdomain II) corresponds to an invariant Lys among tyrosine kinases thought to be critical for the phosphotransfer reaction. Signature regions indicative of substrate specificity suggest that HpTK5 is a tyrosine rather than a serine/threonine kinase. These include the sequence at positions 740-745 in subdomain VI and the sequence at positions 783-790 in subdomain VIII. Tyrosine residues at positions 601, 619 and 741 are possible substrates for tyrosine kinase activity.

The predicted amino acid sequence of HpTK5 most closely resembles that of the subfamily originally defined by *EPH*. The pattern of expression of the *EPH* subfamily is suggestive of a role in differentiation and development. In particular, the emergence of neural elements corresponds with the expression of certain *EPH*-related genes. The *EPH* family receptors, Hek2 and Elk, are the most closely related pTKs to HpTK5. They share 79.3 and 76.5% identity within the ICD respectively and 45 and 42% identity within the ECD respectively.

B. Chromosome Mapping of HpTK5

Somatic cell hybrid DNAs from a panel of 25 human-hamster cell lines (Bios, New Haven, CN) were used for chromosome localization by PCR. Two sets of primers from the 3' untranslated region of HpTK5 were chosen. PCR was performed with 250 ng DNA and 50 pmol each of the 5' and 3' primers, 50 mM KCl, 1.5mM MgCl₂, 20 µg/ml gelatin, 0.2 mM dNTPs and 2.5 units Taq polymerase in a final volume of 100 µl. Cycles of 94°C for 30 sec, 60°C for 30 sec and 72°C for 30 sec were repeated 30 times. A portion of each sample (15 µl) was electrophoresed through a 1.5% agarose gel, transferred to a nylon membrane and hybridized to a ³²P-labelled full length HpTK5 cDNA probe prior to 5 hour autoradiography. Positives were scored and compared to a matrix summary of human chromosomal material present in each of the somatic cell hybrid DNAs.

The 3'-untranslated region characteristically contains few, if any, intervening sequences and has a high degree of diversity among members

of gene families making it preferred in this type of analysis. Both sets of primers gave results that were consistent with human chromosome 7 only. Human chromosome 7 also includes the genes for the EGF receptor, hepatocyte growth factor (HGF) receptor, HGF, platelet-derived growth factor (PDGF) and interleukin-6. Karyotypic abnormalities involving this chromosome are common among human leukemias, particularly in aggressive myeloid leukemias that occur following radiation, alkylating agent chemotherapy or a pre-existing myelodysplastic condition (Baer et al., Curr. Opin. Oncol. 4:24-32 [1992]).

10 C. Northern Blotting of HpTK5

Poly-A selected RNA was electrophoresed through a 1.2% agarose, 2.2M formaldehyde gel and transferred to a nylon filter. Prepared or commercially obtained filters were hybridized in 50% formamide at 42°C to ³²-P labeled HpTK5, glyceraldehyde-3-phosphate dehydrogenase (GAPDH) or actin cDNA inserts and washed under stringent conditions (final wash: 0.1 x SSC, 0.2% SDS at 65°C). SSC is 0.15 M NaCl/ 0.015M Na₃citrate, pH 7.6. Northern blots of human fetal or adult tissue RNA were obtained from Clontech (Palo Alto, CA) and contained 2 µg/lane of poly A selected RNA.

Northern blot analysis of human fetal tissues revealed a single transcript of ~4Kb in heart, lung, liver and kidney, with a lesser signal detectable in brain. In adult human tissue, no signal was detectable in brain, while placenta had a particularly intense signal followed by kidney, liver, lung and pancreas. Skeletal muscle and heart were of lower signal intensity.

25 HpTK5 expression in human tumor cell lines was also analyzed by Northern blot analysis performed as discussed above. Cell lines derived from liver, breast (MCF 7), colon (Colo 205), lung (NCI 69), melanocyte (HM-1) or cervix (HeLa) had detectable signal of appropriate size. Message was present in select cell lines of hematopoietic origin. K562 (a primitive myeloid cell with multipotential), THP-1 (a monocytoid cell), U937 (a myelomonocytic cell line), Hep3B (a human hepatocarcinoma cell line), and CMK (of megakaryocytic origin) were all positive for HpTK5 message, but lymphoid (H9, Jurkat, JH-1, Raji, Ramos) or select other myeloid cells (KG-1 or KMT2) had no detectable transcript by
30 Northern analysis.

Differential expression of the HpTK5 transcript in fetal versus adult brain suggests that HpTK5 may share, with other EPH subfamily

members, a role in events related to neural development. However, unlike some members of the EPH subfamily which are exclusively expressed in neurons (Maisonpierre et al., supra), HpTK5 is widely expressed in other tissues. In particular, HpTK5 is expressed in hematopoietic cells including CD34+ hematopoietic progenitor cells. The presence of the HpTK5 message in early hematopoietic cells and cell lines of myeloid lineage, but not in cell lines derived from lymphoid cells, suggests that HpTK5 may have lineage restricted expression.

EXAMPLE 3

10 PRODUCTION OF POLYCLONAL ANTIBODIES TO HPTK5

An HpTK5 extracellular domain (ECD)-human IgG₁ Fc fusion gene was constructed and fusion protein produced as previously described (Bennett et al., J. Biol. Chem. 266:23060-23067 [1991]). Polyclonal antibodies were generated in New Zealand White rabbits against the fusion protein; 4µg in 100µL PBS was emulsified with 100µL Freund's adjuvant (complete adjuvant for the primary injection and incomplete adjuvant for all boosts). For the primary immunization and the first boost, the protein was injected directly into the popliteal lymph nodes (Sigel et al., Methods Enzymol. 93:3-12 [1983]). For subsequent boosts, the protein was injected into subcutaneous and intramuscular sites. 1.3 µg protein/kg body weight was injected every 3 weeks with bleeds taken 1 and 2 weeks following each boost. HpTK5 specificity of the immunized rabbit serum was assessed by flow cytometric analysis of NIH3T3 cells transfected with full length HpTK5 or vector alone using a 1:200 dilution of pre-immune serum or anti-HpTK5-IgG Fc serum. Significant peak shifts were observed in several HpTK5 expressing clones as compared to either pre-immune serum or vector alone transfectant controls.

EXAMPLE 4

UTILITY AND AGONIST ACTIVITY OF POLYCLONAL ANTIBODIES TO HPTK5

30 A. FLAG-HpTK5 Fusion Construct

Overlapping oligonucleotides encoding a 12 amino acid peptide having the sequence MDYKDDDDKKLAM (SEQ ID NO: 39) which includes the 4 amino acid antibody recognition site "FLAG" (IBI, New Haven, CT) a 5'-EcoRV restriction site and a 3'-NcoI restriction site

(5'-CCGGATATCATGGACTACAAGGACGACGATGACAAGAAGCTTGCCATGGAGCTC; SEQ ID NO: 40), were ligated into the NcoI site (base 88) of HpTK5 in the EcoRV digested Bluescript (Stratagene, La Jolla, CA) vector.

B. In vitro Transcription and Translation

5 Transcription was performed on 2 pmol of linearized HpTK5 or FLAG-HpTK5 containing plasmid at 37°C for 1 h in 50 µl volume containing 10 mM dithiothreitol, 2.5 µg bovine serum albumin, 0.25 mM each dNTP, 0.5 M m7GRNA cap (New England Biolabs, Beverly, MA), 2.5 units RNasin (Promega, Madison, WI), 3 units T3 RNA polymerase (Pharmacia, Piscataway, 10 NJ). 1 µg of DNAase (New England Biolabs, Beverly MA) was added for 15 min at 37°C prior to phenol/chloroform extraction and ethanol precipitation. Translation was performed using the Promega rabbit reticulocyte lysate kit according to the manufacturer's specifications with or without ³⁵S-methionine (350 µCi) labeling. Sample buffer 15 containing SDS and beta-mercaptoethanol (2-ME) was added before boiling and 10% SDS-PAGE.

C. HpTK5 Expression in NIH3T3 Cells

A 4038 bp ClaI - XbaI cDNA fragment containing 32 bp of linker sequence, 37 bp of pBluescript (Stratagene La Jolla, CA) polylinker and 20 the entire 3969 bp HpTK5 cDNA was subcloned into the expression vector pRIS (Genentech, Inc.) under the control of the Rous sarcoma virus LTR promoter. NIH3T3 cells maintained in high glucose Dulbecco's Modified Eagle's Medium (DMEM) supplemented with 10% FCS were co-transfected with pRIS-HpTK5 and pNeo (an SV40 based vector containing the neomycin 25 resistance marker) by the calcium phosphate method as described by Gorman et al., in DNA Prot. Engineer. Tech. 2:3-10 [1990]. Neomycin resistant colonies were selected 48 hours after transfection with Geneticin (Gibco/BRL) at 400 µg/ml. Fourteen days later individual resistant colonies were isolated, expanded and analyzed by flow cytometry for HpTK5 30 expression using rabbit polyclonal antiserum.

D. Immunoprecipitation

Cells (Hep3B, control NIH3T3 or HpTK5 transfected NIH3T3) or in vitro translated protein (HpTK5 or FLAG-HpTK5) were used for immunoprecipitation with either serum (pre-immune or anti-HpTK5-IgG Fc) 35 or monoclonal antibody (FLAG-specific, M2, or isotype control) (IBI,

Rochester, NY). Subconfluent cells were labeled with 200 μ Ci/ml 35 S-methionine for 18 hours and lysed in lysis buffer (150 mM NaCl, 50 mM Tris-HCl pH8.0, 1 mM EDTA, 0.025 Na azide, 1% NP-40, 0.1% SDS, 10% Glycerol, 0.5% Na deoxycholate, 1 mM phenylmethylsulfonyl flouride (PMSF), 10 μ g/ml aprotinin, 10 μ g/ml leupeptin and 50 μ M Na vanadate) for 5 30 min on ice. The cell lysate was centrifuged (12,000 X g) for 10 min at 4°C. Cell lysate supernatant or *in vitro* translation mixture was precleared with 0.05 volume of normal rabbit serum and adsorbed with 0.05 volume of Staphylococcus aureus protein-A Sepharose CL4B. After 10 centrifugation, preimmune or immune serum (1:100 dilution), or monoclonal antibody, was added and rocked overnight at 4°C before 100 μ l of protein-A Sepharose CL4B was added and the solution rocked 4°C for additional 2 h. Immunoprecipitates were washed, suspended in SDS/PAGE loading buffer (10% glycerol, 5% 2-ME, 2.3% SDS and 62.5mM Tris-HCl pH 6.8), heated to 15 95°C for 5 min and analyzed by 7.5% SDS-PAGE.

E. Cell Fractionation

Cell fractionation of Hep3B cells was performed to confirm the membrane localization of HpTK5 predicted by its amino acid sequence. Hep-3B cells (1×10^7) were labeled with 200 μ Ci/ml 35 S-methionine in alpha MEM 20 medium containing 10% dialyzed FCS overnight. The cells were washed twice with cold PBS, scraped into 1ml of cold buffer (20mM Tris-HCl pH 7.5, 2mM EDTA, 5mM EGTA, 0.25M sucrose, 0.01% leupeptin, 4mM PMSF, 10mM 2-ME) and disrupted by sonication for 40 seconds. Whole homogenates were centrifuged at 12,000 X g for 15 min, the nuclear pellets isolated and 25 the decanted supernatant centrifuged at 140,000 X g for 40 min at 4°C to pellet membranes. The resultant supernatant served as the cytosolic (C) fraction. Nuclear (N) and membrane (M) fractions were washed and dissolved in buffer containing 0.5% NP-40 prior to immunoprecipitation. The C, N or M fractions were immunoprecipitated with an anti-HpTK5 or 30 pre-immune (control) serum, subjected to 12% SDS-PAGE and autoradiographed. HpTK5 segregated predominantly with the membrane fraction, though immunoprecipitated material was evident to a lesser extent in cytosol.

F. Protein Kinase Assay

35 Immunoprecipitates were washed once with kinase buffer (25mM Hepes pH7.4, 1mM DTT, 10mM MgCl, 10mM MnCl), and resuspended in 40 μ l of kinase

buffer containing either unlabeled ATP or 10 μ Ci of ³²P-ATP (3000Ci/mM). After a 10min incubation at 30°C, the reaction was stopped by adding 40 μ l of 2 X sample buffer and boiling the samples for 3min prior to electrophoresis on 8.0% SDS-PAGE gel. The dried gel was covered with 4
5 sheets of aluminum foil to block ³⁵S-labelled protein autoradiography and the gel was placed under film for 5 hours to overnight.

G. Western Blotting and Phosphotyrosine Assay

Proteins were electrophoretically transferred to a 0.2 μ m nitrocellulose (Bio-Rad) or a 0.45 μ m polyvinylidene difluoride
10 (Millipore) membrane in a buffer containing 25 mM Tris-HCl (pH 7.5), 192 mM glycine and 20% methanol at 100 mA for 2 h. Filters were washed in TBS (10 mM Tris-HCl pH 8.0, 150 mM NaCl) blocked by incubating in TBST (TBS with 0.05% Tween-20) plus 5% BSA overnight. Filters were washed
15 four times for 5 min each in TBST and incubated for 2 h with 4G10 anti-phosphotyrosine antibody from UBI (1:1000 dilution in TBST). Filters were washed four times for 5 min each in TBST and incubated for 1 h with the alkaline phosphatase labelled anti-mouse secondary antibody (Promega) at a 1:7500 dilution in TBST. After washing four times, the blot was developed for 30-60 min in AP buffer (100mM Tris-HCl, 100 mM NaCl, 5 mM
20 MgCl₂) plus BCIP, NBT substrates.

H. Antibody Induced Phosphorylation Assay

Rabbit antisera to HpTK5-IgG Fc were tested for their ability to induce HpTK5 phosphorylation in HpTK5 transfected NIH3T3 cells. Cells were plated at a density of 5 x 10⁵ cells/well in a 6-well plate and,
25 after 24 hours, were serum starved for 1 hour prior to adding pre-immune or immune serum at a 1:50 dilution for 30 minutes. Cells were then washed in PBS and lysed in either 2X sample buffer or NP-40 lysis buffer as described above. Either crude lysates or immunoprecipitated cell lysates were then separated via 4-12% gradient SDS-PAGE and analyzed by
30 anti-phosphotyrosine immunoblot as described above. HpTK5 expressing cells were exposed to antisera and separated by SDS-PAGE either with or without immunoprecipitation. The electrotransferred gel was immunoblotted with anti-phosphotyrosine antibody. Enhanced tyrosine phosphorylation of HpTK5 was observed following exposure to polyclonal antiserum showing an
35 agonist-like effect of antibody binding. Interaction of HpTK5 with an antibody directed against its ECD induces phosphorylation. This provides

further support that HpTK5 may serve as a receptor for a ligand that triggers kinase activation. Details of the signaling pathway of HpTK5 may be further explored using antisera as a surrogate ligand.

I. Conclusions

5 An HpTK5 ECD-IgG Fc fusion protein was expressed, purified and used to generate rabbit anti-serum which immunoprecipitated a 120kD protein from Hep3B cells. The specificity of the antiserum was confirmed by immunoprecipitation of *in vitro* translated HpTK5 RNA and HpTK5 transfected NIH3T3 cells. To determine the functional capacity of HpTK5, 10 *in vitro* translated HpTK5 was immunoprecipitated, exposed to kinase conditions and immunoblotted using a phosphotyrosine specific monoclonal antibody. The data obtained indicated that HpTK5 is phosphorylated on tyrosine. However, the presence of other bands consistently appearing in the ³²P-labelled immunoprecipitation suggested that HpTK5 protein was 15 only partially purified and therefore, it could not be concluded that HpTK5 was enzymatically active. To overcome this problem, a fusion construct was generated in which an 8 amino acid epitope (FLAG) was added to the N-terminus of HpTK5. The FLAG-HpTK5 fusion was *in vitro* translated and immunoprecipitated with a FLAG-specific monoclonal 20 antibody resulting in a single protein of appropriate size (~120kD). When subjected to kinase conditions in the presence of ³²P-ATP, the HpTK5-FLAG fusion protein was labelled on tyrosine confirming tyrosine autophosphorylation and thereby, the kinase function of HpTK5.

EXAMPLE 5

25 PRODUCTION OF MONOCLONAL ANTIBODIES TO HPTK5

Anti-HpTK5 monoclonal antibodies were produced by hyperimmunizing BALB/c mice intraperitoneally with the HpTK5 extracellular domain (ECD)-human IgG₁ Fc fusion protein (produced using the techniques disclosed above) in RIBI adjuvant (RIBI ImmunoChem Research, Hamilton, MT) and 30 fusing splenocytes with the mouse myeloma cell line X63-Ag8.653 (Kearney et al., J. Immunol. 123:1548-1550 [1979]). The antibodies were purified from ascites fluid using protein A-Sepharose (Repligen Corp., Cambridge, MA) and established affinity chromatography methods (Goding, J.W., J. Immunol. Methods 20:241-253 [1978]).

35 Monoclonal antibodies were screened for their ability to bind the HpTK5 antigen. Starting on day 15 post fusion, culture supernatants were

harvested from the fusion plates and assayed for their ability to specifically "capture" HpTK5-IgG. In this ELISA assay, goat anti-mouse IgG was coated onto 96 well microtiter plates. The culture supernatants (100 μ l) were added to the wells and the mouse IgG present was bound by the goat anti-mouse IgG antibodies. The plates were washed and either HpTK5-IgG or CD4-IgG (100 μ l at 6nM) was added. The "captured" immunoadhesin was detected using a goat anti-hu (Fc specific) horseradish peroxidase conjugate and orthophenylene diamine substrate. Quantitation of substrate catalysis was determined by optical density at 490nm.

Agonist antibodies were then screened for using the techniques disclosed in Example 6 below. Two agonist monoclonal antibodies were identified, one of which has been deposited with the ATCC.

EXAMPLE 6

AGONIST ACTIVITY OF MONOCLONAL ANTIBODIES TO HPTK5

The monoclonal antibodies produced using the techniques disclosed in Example 5 were tested for their ability to induce HpTK5 phosphorylation in HpTK5 transfected NIH3T3 cells. Cells were plated at a density of 5 x 10⁵ cells/well in a 6-well plate and, after 24 hours, were serum starved for 1 hour prior to adding pre-immune serum or anti-HpTK5 monoclonal antibody (undiluted conditioned hybridoma media was used) for 30 minutes. Cells were then washed in PBS and lysed in either 2X sample buffer or NP-40 lysis buffer as described above. Either crude lysates or immunoprecipitated cell lysates were then separated via 4-12% gradient SDS-PAGE and analyzed by anti-phosphotyrosine immunoblot as described above. HpTK5 expressing cells were exposed to the monoclonal antibody and separated by SDS-PAGE either with or without immunoprecipitation. The electrotransferred gel was immunoblotted with anti-phosphotyrosine antibody. Enhanced tyrosine phosphorylation of HpTK5 was observed following exposure to monoclonal antibodies showing an agonist-like effect of antibody binding. Accordingly, interaction of HpTK5 with a monoclonal antibody directed against its ECD is able to induce phosphorylation of the kinase domain thereof.

EXAMPLE 7

PRODUCTION OF POLYCLONAL ANTIBODIES TO SAL-S1

A SAL-S1 extracellular domain (ECD)-human IgG₁ Fc fusion gene was constructed and fusion protein produced as previously described in

Bennett et al., J. Biol. Chem. 266:23060-23067 [1991]. Briefly, PCR primers otk 1.41.1 (SEQ ID NO: 43) and otk 1.41.2 (SEQ ID NO: 44) were employed in the PCR technique using plasmid pRK5.tk1-1.1 (SEQ ID NO: 45) containing SAL-S1 nucleic acid as a template to create a DNA fragment which, when digested with SalI/BstEII, generated an 155bp SalI/BstEII fragment. This 155bp fragment was combined with a 6839bp SalI/HindIII fragment isolated from pRK5.tk1-1.1 and a 719 bp BstEII/HindIII fragment isolated from pBSSK-CH2-CH3 (Bennett et al., supra). These fragments were ligated together to create a plasmid pRK5.tk1.ig1.1 (7713bp in size) which, when transfected into 293 cells, was used to produce a SAL-S1 extracellular domain (ECD)-human IgG Fc fusion protein. Fusion protein was prepared and purified as described in Bennett et al., supra. Polyclonal antibodies were generated in female New Zealand White rabbits against the fusion protein. Briefly, 12.5µg of fusion protein in 0.625ml PBS was emulsified with 0.625ml Freund's adjuvant (complete adjuvant for the primary injection and incomplete adjuvant for all boosts). The primary injection and all boosts were intramuscular at two sites and subcutaneous at multiple sites. Boosts were carried out at 3 week intervals with bleeds taken 1 and 2 weeks following each boost. SAL-S1 specificity of the immunized rabbit serum was assessed by flow cytometric analysis of 293 (ATCC CRL 1593) and COS7 (ATCC CRL 1651) cells transfected with full length SAL-S1 or vector alone (see below) using a 1:200 dilution of pre-immune serum or anti-SAL-S1-IgG Fc serum. Significant peak shifts were observed in several SAL-S1 expressing clones as compared to either pre-immune serum or vector alone transfectant controls.

EXAMPLE 8

UTILITY AND AGONIST ACTIVITY OF SAL-S1 POLYCLONAL ANTIBODIES

A. Immunoprecipitation

Control 293 and COS7 cells as well as SAL-S1 transfected 293 and COS7 cells were used for immunoprecipitation with either pre-immune serum or anti-SAL-S1-IgG Fc polyclonal antibody. COS7 and 293 cells were transfected using a CaPO₄ procedure as described by Gorman, C. DNA Cloning, Glover D. Ed., IRL Press, Oxford, vol2: 143-190 (1985). For transient expression, 293 cells were transfected as described by Gearing et al. EMBO 8: 3667-3676 (1989). Subconfluent cells were labeled with 200µCi/ml ³⁵S- methionine for 18 hours and lysed in lysis buffer (150 mM

NaCl, 50mM HEPES, pH 7.5, 1 mM EGTA, 0.025 Na azide, 1% Triton-X 100, 1.5mM MgCl₂, 10% Glycerol, 1 mM phenylmethylsulfonyl flouride [PMSF], 10 µg/ml aprotinin, 10 µg/ml leupeptin and 50 µM Na vanadate) for 10 min on ice. The cell lysate was centrifuged (12,000 X g) for 10 min at 4°C.

5 After centrifugation, preimmune or polyclonal antibody was added to the supernatant and rocked for 4 hrs at 4°C before 100 µl of protein-A Sepharose CL4B was added and the solution rocked 4°C for additional 2 h. Immunoprecipitates were washed, suspended in SDS/PAGE loading buffer (10% glycerol, 5% 2-ME, 2.3% SDS and 62.5mM Tris-HCl pH 6.8), heated to 95°C

10 for 5 min and analyzed by 7.5% SDS-PAGE.

B. Western Blotting and Phosphotyrosine Assay

Proteins were electrophoretically transferred to a 0.2 µm nitrocellulose (Bio-Rad) or a 0.45µm polyvinylidene difluoride (Millipore) membrane in a buffer containing 25 mM Tris-HCl (pH 7.5), 192

15 mM glycine and 20% methanol at 100 mA for 2 h. Filters were washed in TBS (10 mM Tris-HCl pH 8.0, 150 mM NaCl) blocked by incubating in TBST (TBS with 0.05% Tween-20) plus 5% BSA overnight. Filters were washed four times for 5 min each in TBST and incubated for 2 h with 4G10 anti-phosphotyrosine antibody from UBI (1:1000 dilution in TBST). Filters

20 were washed four times for 5 min each in TBST and incubated for 1 h with the alkaline phosphatase labelled anti-mouse secondary antibody (Promega) at a 1:5000 dilution in TBST. After washing four times, the blot was developed for 30-60 min in AP buffer (100mM Tris-HCl, 100 mM NaCl, 5 mM MgCl₂) plus BCIP, NBT substrates.

25 C. Antibody Induced Phosphorylation Assay

Rabbit antisera to SAL-S1-IgG Fc were tested for their ability to induce SAL-S1 phosphorylation in SAL-S1 transfected 293 cells. Cells were plated at a density of 5 x 10⁵ cells/well in a 6-well plate and, after 24 hours, were serum starved for 12 hours prior to adding pre-immune or

30 immune serum at a 1:5 dilution for 30 minutes. Cells were then washed in PBS and lysed in either sample buffer or Triton-X lysis buffer as described above. Either crude lysates or immunoprecipitated cell lysates were then separated via 8% or 4-12% gradient SDS-PAGE and analyzed by anti-phosphotyrosine immunoblot as described above. SAL-S1 expressing

35 cells were exposed to antisera and separated by SDS-PAGE either with or without immunoprecipitation. The electrotransferred gel was immunoblotted

with anti-phosphotyrosine antibody. Enhanced tyrosine phosphorylation of SAL-S1 was observed following exposure to polyclonal antiserum showing an agonist-like effect of antibody binding. Interaction of SAL-S1 with an antibody directed against its ECD induces phosphorylation.

5

EXAMPLE 9PRODUCTION OF MONOCLONAL ANTIBODIES TO SAL-S1

Anti-SAL-S1 monoclonal antibodies were produced by hyperimmunizing BALB/c mice in the foot pad with the SAL-S1 extracellular domain-human IgG₁ Fc fusion protein in RIBI adjuvant (RIBI Immunochem Research, Hamilton, MT) and fusing lymphocyte from lymph nodes with the mouse myeloma cell line X63-Ag8U1.

Starting on day 10 post fusion, cultured supernatants were harvest from the fusion plates and assayed for their ability to bind to SAL-S1. In this ELISA assay, SAL-S1 IgG₁ was coated onto 96 microtiter plates. The cultured supernatants (100μl) were added to the wells and the mouse antibodies present were bound to Sal-S1 IgG₁. The plates were washed and mouse IgG was detected using a goat anti-mouse IgG (Fc specific with no cross reactivity against human IgG Fc) horseradish peroxidase conjugate and orthophenylene diamine substrate. Quantitation of substrate catalysis was determined by optical density at 490 nm.

Cultured supernatants which were positive from ELISA were then tested for their ability to specifically bind to 293 transfected with SAL-S1 receptor and analyzed by flow cytometry. Agonist antibodies were then screened for using the techniques disclosed in Example 10 below. Six agonist monoclonal antibodies were identified.

EXAMPLE 10AGONIST ACTIVITY OF MONOCLONAL ANTIBODIES TO SAL-S1

The monoclonal antibodies were tested for their ability to induce SAL-S1 phosphorylation in SAL-S1 transfected 293 cells. Cells were harvested from tissue culture dish by assay buffer and washed 2x with the same buffer. 1x10⁵ cells were added to a 96 U-bottom plate which was centrifuged and assay buffer was removed. 150 μl of cultured supernatants was added to each well followed by incubation at 37°C for 30 minutes, the plate was centrifuged and cultured supernatants were removed. 100 μl of Fixing solution was added, the cells were fixed for 30 minutes at -20°C, cells were washed with buffer 2x and stained with anti-phosphotyrosine

conjugate with FITC for 60 minutes at 4°C. Cells were analyzed by flow cytometry (FACScan Becton Dickinson, Milpitas, CA). The six anti-SAL-S1 monoclonal antibodies were able to induce SAL-S1 phosphorylation in SAL-S1 transfected 293 cells.

5

Deposit of Materials

The following culture has been deposited with the American Type Culture Collection, 12301 Parklawn Drive, Rockville, MD, USA (ATCC):

<u>Hybridoma</u>	<u>ATCC No.</u>	<u>Deposit Date</u>
Anti-HpTK5	HB 11,583	March 15, 1994

10 This deposit was made under the provisions of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purpose of Patent Procedure and the Regulations thereunder (Budapest Treaty). This assures maintenance of a viable culture for 30 years from the date of deposit. The organism will be made available by ATCC under
15 the terms of the Budapest Treaty, and subject to an agreement between Genentech, Inc. and ATCC, which assures permanent and unrestricted availability of the progeny of the culture to the public upon issuance of the pertinent U.S. patent or upon laying open to the public of any U.S. or foreign patent application, whichever comes first, and assures
20 availability of the progeny to one determined by the U.S. Commissioner of Patents and Trademarks to be entitled thereto according to 35 USC §122 and the Commissioner's rules pursuant thereto (including 37 CFR §1.14 with particular reference to 886 OG 638).

The assignee of the present application has agreed that if the
25 culture on deposit should die or be lost or destroyed when cultivated under suitable conditions, it will be promptly replaced on notification with a viable specimen of the same culture. Availability of the deposited strain is not to be construed as a license to practice the invention in contravention of the rights granted under the authority of
30 any government in accordance with its patent laws.

The foregoing written specification is considered to be sufficient to enable one skilled in the art to practice the invention. The present invention is not to be limited in scope by the culture deposited, since the deposited embodiment is intended as a single illustration of one
35 aspect of the invention and any culture that are functionally equivalent

are within the scope of this invention. The deposit of material herein does not constitute an admission that the written description herein contained is inadequate to enable the practice of any aspect of the invention, including the best mode thereof, nor is it to be construed as
5 limiting the scope of the claims to the specific illustration that it represents. Indeed, various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description and fall within the scope of the appended claims.

10

Equivalents

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

- (i) APPLICANT: Genentech, Inc.
Bennett, Brian D.
5 Goeddel, David
Lee, James M.
Matthews, William
Tsai, Siao Ping
Wood, William I.
- 10 (ii) TITLE OF INVENTION: PROTEIN TYROSINE KINASE AGONIST ANTIBODIES
- (iii) NUMBER OF SEQUENCES: 45
- (iv) CORRESPONDENCE ADDRESS:
(A) ADDRESSEE: Genentech, Inc.
(B) STREET: 460 Point San Bruno Blvd
15 (C) CITY: South San Francisco
(D) STATE: California
(E) COUNTRY: USA
(F) ZIP: 94080
- 20 (v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: 5.25 inch, 360 Kb floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: patin (Genentech)
- 25 (vi) CURRENT APPLICATION DATA:
(A) APPLICATION NUMBER:
(B) FILING DATE:
(C) CLASSIFICATION:
- (vii) PRIOR APPLICATION DATA:
(A) APPLICATION NUMBER: 08/222616
30 (B) FILING DATE: 04-APR-1994
- (viii) ATTORNEY/AGENT INFORMATION:
(A) NAME: Wendy M. Lee
(B) REGISTRATION NUMBER: 00,000
(C) REFERENCE/DOCKET NUMBER: 821P3PCT
- 35 (ix) TELECOMMUNICATION INFORMATION:
(A) TELEPHONE: 415/225-1994
(B) TELEFAX: 415/952-9881
(C) TELEX: 910/371-7168

(2) INFORMATION FOR SEQ ID NO:1:

- 40 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

CGGATCCACA GNGACCT 17

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:

- 5 (A) LENGTH: 23 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

10 GGAATTCCAA AGGACCAGAC GTC 23

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:

- 15 (A) LENGTH: 21 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

CGGATCCATC CACAGAGATG T 21

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:

- 20 (A) LENGTH: 26 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

25 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

GGAATTCCTT CAGGAGCCAT CCACTT 26

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:

- 30 (A) LENGTH: 160 bases
(B) TYPE: nucleic acid

- (C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

GGATCCTGTG CATCAGTGAC TTAGGGCTAG GAACATTCTG CTGTCGGAAA 50
5 GCGACGTGGT GAAGATCTGT GACTTTGGCC TTGCCCCGGA CATCTACAAA 100
GACCCAGCT ACGTCCGCAA GCATGCCCGG CTGCCCCTGA AGTGGATGGC 150
GCCAGAATTC 160

(2) INFORMATION FOR SEQ ID NO:6:

- (i) SEQUENCE CHARACTERISTICS:
10 (A) LENGTH: 53 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

15 Asp Pro Val His Gln Xaa Leu Arg Ala Arg Asn Ile Leu Leu Ser
1 5 10 15
Glu Ser Asp Val Val Lys Ile Cys Asp Phe Gly Leu Ala Arg Asp
20 25 30
Ile Tyr Lys Asp Pro Ser Tyr Val Arg Lys His Ala Arg Leu Pro
35 40 45
20 Leu Lys Trp Met Ala Pro Glu Phe
50 53

(2) INFORMATION FOR SEQ ID NO:7:

- (i) SEQUENCE CHARACTERISTICS:
25 (A) LENGTH: 147 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

GGATCCATTC ACAGAGACCT AGCAGCACGC AACATCCTGG TCTCAGAGGA 50
30 CCTGGTAACC AAGGTCAGCG ACTTTGGCCT GGCCAAAGCC GAGCGGAAGG 100

GGCTAGACTC AAGCCGGCTG CCCGTCAAAT GGATGGCTCC CGAATTC 147

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:

- 5 (A) LENGTH: 49 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

	Gly	Ser	Ile	His	Arg	Asp	Leu	Ala	Ala	Arg	Asn	Ile	Leu	Val	Ser
	1				5					10					15
10	Glu	Asp	Leu	Val	Thr	Lys	Val	Ser	Asp	Phe	Gly	Leu	Ala	Lys	Ala
					20					25					30
	Glu	Arg	Lys	Gly	Leu	Asp	Ser	Ser	Arg	Leu	Pro	Val	Lys	Trp	Met
					35					40					45
15	Ala	Pro	Glu	Phe											
					49										

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:

- 20 (A) LENGTH: 149 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

GTTGGAATTC CTTCCGGCGC CATCCATTTT ACCGGCAGCT TTATTTCTGTG 50

TCTAGATTCA TAGATGTCTT CATTATCTAC CTTAAAAACT CTGGCAAGTC 100

25 CAAATCTGC TACTTTGTAG ATATTATGTT CACCAACGAG GACATTCCT 149

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:

- 30 (A) LENGTH: 47 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

	Val	Gly	Ile	Pro	Ser	Gly	Ala	Ile	His	Phe	Thr	Gly	Ser	Phe	Ile
	1				5					10					15

Ser Cys Leu Asp Ser Met Ser Ser Leu Ser Thr Leu Lys Thr Leu
 20 25 30

Ala Ser Pro Lys Ser Ala Thr Leu Ile Leu Cys Ser Pro Thr Arg
 35 40 45

5 Thr Phe
 47

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:

- 10 (A) LENGTH: 151 bases
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

GTGCACAGGG ATCTCGCGGC TCGGAACATC CTCGTCGGGG AAAACACCCT 50

15 CTCGAAAGTT GGGGACTTCG GGTTAGCCAG GCTTATCAAG GAGGACGTCT 100

ACCTCTCCCA TGACCACAAT ATCCCCTACA AATGGATGGC CCCTGAGGGA 150

A 151

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:

- 20 (A) LENGTH: 50 amino acids
 (B) TYPE: amino acid
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

25 Val His Arg Asp Leu Ala Ala Arg Asn Ile Leu Val Gly Glu Asn
 1 5 10 15

Thr Leu Ser Lys Val Gly Asp Phe Gly Leu Ala Arg Leu Ile Lys
 20 25 30

Glu Asp Val Tyr Leu Ser His Asp His Asn Ile Pro Tyr Lys Trp
 35 40 45

30 Met Ala Pro Glu Gly
 50

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 137 bases
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

5 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

GTTCAACGAG ATCTCAAGTC CAACAACATT TTGCTGCTGC AGCCCATTGA 50
 GAGTGACGAC ATGGAGCACA AGACCCTGAA GATCACCAGAC TTTGGCCTGG 100
 CCCGAGAGTG GCACAAAACC ACACAAATGA GTGCCGC 137

(2) INFORMATION FOR SEQ ID NO:14:

- 10 (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 45 amino acids
 - (B) TYPE: amino acid
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

15	Val	His	Arg	Asp	Leu	Lys	Ser	Asn	Asn	Ile	Leu	Leu	Leu	Gln	Pro
	1				5					10				15	
	Ile	Glu	Ser	Asp	Asp	Met	Glu	His	Lys	Thr	Leu	Lys	Ile	Thr	Asp
					20					25				30	
20	Phe	Gly	Leu	Ala	Arg	Glu	Trp	His	Lys	Thr	Thr	Gln	Met	Ser	Ala
					35					40				45	

(2) INFORMATION FOR SEQ ID NO:15:

- 25 (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 211 bases
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

GTCAATCGTG ACCTCGCCGC CCGAAATGTG TTGCTAGTTA CCCAACATTA 50
 CGCCAAGATC AGTGATTTCG GACTTTCCAA AGCACTGCGT GCTGATGAAA 100
 30 ACTACTACAA GGCCCAGACC CATGGAAAGT GGCCTGTCAA GTGGTACGCT 150

CCGGAATGCA TCAACTACTA CAAGTTCTCC AGCAAAAGCG ATGTCTGGTC 200

CTTTGGAATT C 211

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:

- 5 (A) LENGTH: 70 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

10	Val	Asn	Arg	Asp	Leu	Ala	Ala	Arg	Asn	Val	Leu	Leu	Val	Thr	Gln
	1				5					10					15
	His	Tyr	Ala	Lys	Ile	Ser	Asp	Phe	Gly	Leu	Ser	Lys	Ala	Leu	Arg
					20					25					30
	Ala	Asp	Glu	Asn	Tyr	Tyr	Lys	Ala	Gln	Thr	His	Gly	Lys	Trp	Pro
					35					40					45
15	Val	Lys	Trp	Tyr	Ala	Pro	Glu	Cys	Ile	Asn	Tyr	Tyr	Lys	Phe	Ser
					50					55					60
	Ser	Lys	Ser	Asp	Val	Trp	Ser	Phe	Gly	Ile					
					65					70					

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:

- 20 (A) LENGTH: 6827 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

25 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

TTCGAGCTCG CCCGACATTG ATTATTGACT AGTTATTAAT AGTAATCAAT 50

TACGGGGTCA TTAGTTCATA GCCCATATAT GGAGTTCCGC GTTACATAAC 100

TTACGGTAAA TGGCCCGCCT GGCTGACCGC CCAACGACCC CCGCCCATTG 150

ACGTCAATAA TGACGTATGT TCCCATAGTA ACGCCAATAG GGACTTTCCA 200

30 TTGACGTCAA TGGGTGGAGT ATTTACGGTA AACTGCCCAC TTGGCAGTAC 250

ATCAAGTGTA TCATATGCCA AGTACGCCCC CTATTGACGT CAATGACGGT 300

AAATGGCCCG CCTGGCATTG TGCCCAGTAC ATGACCTTAT GGGACTTTCC 350

TACTTGGCAG TACATCTACG TATTAGTCAT CGCTATTACC ATGGTGATGC 400

GGTTTTGGCA GTACATCAAT GGGCGTGGAT AGCGGTTTGA CTCACGGGGA 450

5 TTTCCAAGTC TCCACCCCAT TGACGTCAAT GGGAGTTTGT TTTGGCACCA 500

AAATCAACGG GACTTTCCAA AATGTCGTAA CAACTCCGCC CCATTGACGC 550

AAATGGGCGG TAGGCGTGTA CGGTGGGAGG TCTATATAAG CAGAGCTCGT 600

TTAGTGAACC GTCAGATCGC CTGGAGACGC CATCCACGCT GTTTTGACCT 650

CCATAGAAGA CACCGGGACC GATCCAGCCT CCGCGGCCCG GAACGGTGCA 700

10 TTGGAACGCG GATTCCCCGT GCCAAGAGTG ACGTAAGTAC CGCCTATAGA 750

GTCTATAGGC CCACTTGGCT TCGTTAGAAC GCGGCTACAA TTAATACATA 800

ACCTTATGTA TCATACACAT ACGATTTAGG TGAACTATA GAATAACATC 850

CACTTGCCT TTCTCTCCAC AGGTGTCCAC TCCCAGGTCC AACTGCACCT 900

CGGTTCTATC GATTGAATTC CCCGGGGATC CTCTAGAGAT CCCTCGACCT 950

15 CGAGATCCAT TGTGCTGGCG CGGATTCTTT ATCACTGATA AGTTGGTGGA 1000

CATATTATGT TTATCAGTGA TAAAGTGTC AAGCATGACAA AGTTGCAGCC 1050

GAATACAGTG ATCCGTGCCG CCCTAGACCT GTTGAACGAG GTCGGCGTAG 1100

ACGGTCTGAC GACACGCAA CTGGCGGAAC GGTGGGGGT TCAGCAGCCG 1150

GCGCTTTACT GGCACCTCAG GAACAAGCGG GCGCTGCTCG ACGCACTGGC 1200

CGAAGCCATG CTGGCGGAGA ATCATAGCAC TTCGGTGCCG AGAGCCGACG 1250

ACGACTGGCG CTCATTTCTG ACTGGGAATG CCCGCAGCTT CAGGCAGGCG 1300

CTGCTCGCCT ACCGCCAGCA CAATGGATCT CGAGGGATCT TCCATACCTA 1350

CCAGTTCTGC GCCTGCAGGT CGCGGCCGCA CTACTCTTTG ATGTATTACT 1400

5 CATATTACCA AGGAATAACT GCGGGGCACA GGGTCAGGTG CTGAAGGGAC 1450

ATTGTGAGAA GTGACCTAGA AGGCAAGAGG TGAGCCCTCT GTCACGCTGG 1500

CATAAGGGCC GCTTGAGGGC TCTTTGGTCA AGCAGTAACG CCAGTGTCTG 1550

GGAAGGCACC TGTTACTCAG CAGACCATGA AAGGGCGTCT CCCTTTCCTT 1600

GGAGCAGTCA GGAACACTC TGCTCCACCA GCTTCTTGTG GGAGCCTGGA 1650

10 TATTATCCAG GCCTGCCCCG AGTCATCCGG AGGCCTAACC CCTCCCTGTG 1700

GTGCTTCAGT GGTCACTC CTTGTCCACT TTCATGCTCC TCTTGGCCTC 1750

CTGTTCCCTC TTGGAAGTTT GTAGTAGATA GCAGAAGAAA TAGCGAAAGT 1800

CTTAAAGTCT TTGATCTTTC TTATAAGTGC AGAGAAGAAA TGCTGACGTA 1850

TGCTGCCCTC TCTCTCTCTG CTTCAGCTAC CTGAAGCCGC TTTCTTGTCT 1900

15 ATACCTGCTC TCTATCTGCT CACACTCCTC CGAGGCCAGC ACCATCCCAC 1950

TGTCTGTCTG GTTGTCCACA GAGCCTTTGT AGGTCGTTGG GGTCATGGGG 2000

AATTCCTCAA ATGTCTTCAT CCTGGAGGAA CCACGGGTCT CAGCCCCTCT 2050

GGCCAGGCAC CCGGAAAGG ACACCCAGTT GTAATACCTG GCGGCCAGGC 2100

TGTGGCGCTG CAGGCTTGGC GGGCTGTCCT CAGCGTCAGC CTGGGCGATG 2150

TGTAGGGCCA TGGTGGACAC CTGCGAGAAG CTGCCCTCTT CTGAGCTCTG 2200

AGAGCTGCGC GGGGCCATGC AGACCTCCTC TTCCTCTTGC AGGCCCCTGC 2250

CCTGGAGCAG GTCCCCCAGG ATCTCCACCA GCTCCGAGAA TGCAGGTCTC 2300

GCCTTGGGGT CTCCGGACCA GCAGTTCAGC ATGATGCGGC GTATGGCGGG 2350

5 AGTGGCCAGC TCCGGGGCCC TCATCCTTGT GCCGTCTCTC AGCCGCTGGC 2400

AGAACTCCTC ATTGATCTGC ACCCCAGGGT ACGGGGAGGC CCCAGAGAG 2450

AAGATCTCCC AGAGAAGCAC CCCAAAGGAC CACACGTCAC TCTGCGTGGT 2500

GTACACCTTG TCGAAGATGC TTTCAGGGGC CATCCACTTC AGGGGCAGCC 2550

GGGCACTGCC CTTGCGGACG TAGTCGGGGT CTTTGTAGAT GTCCCGGGCA 2600

10 AGGCCAAAGT CACAGATCTT CACCACGTCG CTTTCCGACA GCAGAATGTT 2650

CCGAGCAGCC AGGTCTCTGT GGATGCACTT TCGGGAAGCC AGGAACTCCA 2700

TCCCTCTGGC CACCTGGAAG CTGTAGCAGA CAAGATCTTC CATGGTCAGC 2750

GGGCTCAGCC ACAGGTCCTC AGCTTCTTGG TCTGGAGAAG CCCGCCTCGC 2800

TCCGCCCTCG GTCTTCGAGA ACCGCGCGAA GAGGACCCTG TCGCTGCTCC 2850

15 CCGGCCGCCT CCGATCCAGC CTGGCGAGCT CCACCATGGC GCGGAAGCGT 2900

CCGCGCTGCT CGGGAGACTT CTCCTGCGGA TGCACGAAGC TGGCTCGAGG 2950

GCGCCCAGTC GTCCGCCGCA GAGGCGCCTC CATTCCCCCG CCGCCCGCGG 3000

CGCCCCGAG GCCGCCGCT CACCGNGCAG GGGCTGCGGC CGCGACTCTA 3050

GAGTCGACCT GCAGAAGCTT GGCCGCCATG GCCCAACTTG TTTATTGCAG 3100

CTTATAATGG TTACAAATAA AGCAATAGCA TCACAAATTT CACAAATAAA 3150

GCATTTTTTT CACTGCATTC TAGTTGTGGT TTGTCCAAAC TCATCAATGT 3200

ATCTTATCAT GTCTGGATCG ATCGGGAATT AATTCGGCGC AGCACCATGG 3250

CCTGAAATAA CCTCTGAAAG AGGAACTTGG TTAGGTACCT TCTGAGGCGG 3300

5 AAAGAACCAG CTGTGGAATG TGTGTCAGTT AGGGTGTGGA AAGTCCCCAG 3350

GCTCCCCAGC AGGCAGAAGT ATGCAAAGCA TGCATCTCAA TTAGTCAGCA 3400

ACCAGGTGTG GAAAGTCCCC AGGCTCCCCA GCAGGCAGAA GTATGCAAAG 3450

CATGCATCTC AATTAGTCAG CAACCATAGT CCCGCCCTA ACTCCGCCCA 3500

TCCGCCCCCT AACTCCGCC AGTTCCGCC ATTCTCGCC CCATGGCTGA 3550

10 CTAATTTTTT TTATTATGC AGAGCCGAG GCCGCCTCGG CCTCTGAGCT 3600

ATTCCAGAAG TAGTGAGGAG GCTTTTTTGG AGGCCTAGGC TTTTGCAAAA 3650

AGCTGTTAAC AGCTTGGCAC TGGCCGTCGT TTTACAACGT CGTGA CTGGG 3700

AAAACCCTGG CGTTACCCAA CTTAATCGCC TTGCAGACA TCCCCCTTC 3750

GCCAGCTGGC GTAATAGCGA AGAGCCCCGC ACCGATCGCC CTTCCCAACA 3800

15 GTTGCGTAGC CTGAATGGCG AATGGCGCCT GATGCGGTAT TTTCTCCTTA 3850

CGCATCTGTG CGGTATTTCA CACCGCATAC GTCAAAGCAA CCATAGTACG 3900

CGCCCTGTAG CGGCGCATT AAGCGGCGG GTGTGGTGGT TACGCGCAGC 3950

GTGACCGCTA CACTTGCCAG CGCCCTAGCG CCCGCTCCTT TCGCTTTCTT 4000

CCCTTCCTTT CTCGCCACGT TCGCCGGCTT TCCCCGTCAA GCTCTAAATC 4050

GGGGGCTCCC TTTAGGGTTC CGATTTAGTG CTTTACGGCA CCTCGACCCC 4100

AAAAAAGTTG ATTTGGGTGA TGGTTCACGT AGTGGGCCAT CGCCCTGATA 4150

GACGGTTTTT CGCCCTTTGA CGTTGGAGTC CACGTTCTTT AATAGTGGAC 4200

TCTTGTTCCA AACTGGAACA AACTCAACC CTATCTCGGG CTATTCTTTT 4250

5 GATTTATAAG GGATTTTGCC GATTTCGGCC TATTGGTTAA AAAATGAGCT 4300

GATTTAACAA AAATTTAACG CGAATTTTAA CAAAATATTA ACGTTTACAA 4350

TTTTATGGTG CACTCTCAGT ACAATCTGCT CTGATGCCGC ATAGTTAAGC 4400

CAACTCCGCT ATCGCTACGT GACTGGGTCA TGGCTGCGCC CCGACACCCG 4450

CCAACACCCG CTGACGCGCC CTGACGGGCT TGTCTGCTCC CGGCATCCGC 4500

10 TTACAGACAA GCTGTGACCG TCTCCGGGAG CTGCATGTGT CAGAGGTTTT 4550

CACCGTCATC ACCGAAACGC GCGAGGCAGT ATTCTTGAAG ACGAAAGGGC 4600

CTCGTGATAC GCCTATTTTT ATAGGTTAAT GTCATGATAA TAATGGTTTC 4650

TTAGACGTCA GGTGGCACTT TTCGGGGAAA TGTGCGCGGA ACCCCTATTT 4700

GTTTATTTTT CTAAATACAT TCAAATATGT ATCCGCTCAT GAGACAATAA 4750

15 CCCTGATAAA TCTTCAATAA TATTGAAAAA GGAAGAGTAT GAGTATTCAA 4800

ACATTTCCGT GTCGCCCTTA TTCCCTTTTT GCGGCATTT TGCCTTCCTG 4850

TTTTTGCTCA CCCAGAAACG CTGGTGAAAG TAAAGATGC TGAAGATCAG 4900

TTGGGTGCAC GAGTGGGTTA CATCGAACTG GATCTCAACA GCGGTAAGAT 4950

CCTTGAGAGT TTTCGCCCCG AAGAACGTTT TCCAATGATG AGCACTTTTA 5000

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CAACTCGGTC GCCGCATACA CTATTCTCAG AATGACTTGG TTGAGTACTC 5100

ACCAGTCACA GAAAAGCATC TTACGGATGG CATGACAGTA AGAGAATTAT 5150

GCAGTGCTGC CATAACCATG AGTGATAACA CTGCGGCCAA CTTACTTCTG 5200

5 ACAACGATCG GAGGACCGAA GGAGCTAACC GCTTTTTTGC ACAACATGGG 5250

GGATCATGTA ACTCGCCTTG ATCGTTGGGA ACCGGAGCTG AATGAAGCCA 5300

TACCAAACGA CGAGCGTGAC ACCACGATGC CAGCAGCAAT GGCAACAACG 5350

TTGCGCAAAC TATTAAGTGG CGAACTACTT ACTCTAGCTT CCCGGCAACA 5400

ATTAATAGAC TGGATGGAGG CGGATAAAGT TGCAGGACCA CTTCTGCGCT 5450

10 CGGCCCTTCC GGCTGGCTGG TTTATTGCTG ATAAATCTGG AGCCGGTGAG 5500

CGTGGGTCTC GCGGTATCAT TGCAGCACTG GGGCCAGATG GTAAGCCCTC 5550

CCGTATCGTA GTTATCTACA CGACGGGGAG TCAGGCAACT ATGGATGAAC 5600

GAAATAGACA GATCGCTGAG ATAGGTGCCT CACTGATTAA GCATTGGTAA 5650

CTGTCAGACC AAGTTTACTC ATATATACTT TAGATTGATT TAAAACTTCA 5700

15 TTTTAAATTT AAAAGGATCT AGGTGAAGAT CCTTTTTGAT AATCTCATGA 5750

CCAAAATCCC TTAACGTGAG TTTTCGTTCC ACTGAGCGTC AGACCCCGTA 5800

GAAAAGATCA AAGGATCTTC TTGAGATCCT TTTTCTCTGC GCGTAATCTG 5850

CTGCTTGCAA ACAAAAAAAC CACCGCTACC AGCGGTGGTT TGTTTGCCGG 5900

ATCAAGAGCT ACCAACTCTT TTTCCGAAGG TAACTGGCTT CAGCAGAGCG 5950

CAGATACCAA ATACTGTCCT TCTAGTGTAG CCGTAGTTAG GCCACCACTT 6000

CAAGAACTCT GTAGCACCGC CTACATACCT CGCTCTGCTA ATCCTGTTAC 6050

CAGTGGCTGC TGCCAGTGGC GATAAGTCGT GTCTTACCGG GTTGGACTION 6100

AGACGATAGT TACCGGATAA GCGCAGCGG TCGGGCTGAA CCGGGGGTTC 6150

5 GTGCACACAG CCCAGCTTGG AGCGAACGAC CTACACCGAA CTGAGATACC 6200

TACAGCGTGA GCATTGAGAA AGCGCCACGC TTCCCGAAGG GAGAAAGGCG 6250

GACAGGTATC CGGTAAGCGG CAGGGTCGGA ACAGGAGAGC GCACGAGGGA 6300

GCTTCCAGGG GGAAACGCCT GGTATCTTTA TAGTCCTGTC GGGTTTCGCC 6350

ACCTCTGACT TGAGCGTCGA TTTTGTGAT GCTCGTCAGG GGGGCGGAGC 6400

10 CTATGGAAAA ACGCCAGCAA CGCGGCCTTT TTACGGTTCC TGGCCTTTTG 6450

CTGGCCTTTT GCTCACATGT TCTTCTGTC GTTATCCCCT GATTCTGTGG 6500

ATAACCGTAT TACCGCCTTT GAGTGAGCTG ATACCGCTCG CCGCAGCCGA 6550

ACGACCGAGC GCAGCGAGTC AGTGAGCGAG GAAGCGGAAG AGCGCCCAAT 6600

ACGCAAACCG CCTCTCCCCG CGCGTTGGCC GATTCATTAA TCCAGCTGGC 6650

15 ACGACAGGTT TCCCGACTGG AAAGCGGGCA GTGAGCGCAA CGCAATTAAT 6700

GTGAGTTACC TCACTCATTG GGCACCCAG GCTTTACTT TTATGCTTCC 6750

GGCTCGTATG TTGTGTGGAA TTGTGAGCGG ATAACAATTT CACACAGGAA 6800

ACAGCTATGA CCATGATTAC GAATTAA 6827

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 348 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

5 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

	Glu	Lys	Ser	Pro	Glu	Gln	Arg	Gly	Arg	Phe	Arg	Ala	Met	Val	Glu	1	5	10	15
	Leu	Ala	Arg	Leu	Asp	Arg	Arg	Arg	Pro	Gly	Ser	Ser	Asp	Arg	Val	20	25	30	
10	Leu	Phe	Ala	Arg	Phe	Ser	Lys	Thr	Glu	Gly	Gly	Ala	Arg	Arg	Ala	35	40	45	
	Ser	Pro	Asp	Gln	Glu	Ala	Glu	Asp	Leu	Trp	Leu	Ser	Pro	Leu	Thr	50	55	60	
15	Met	Glu	Asp	Leu	Val	Cys	Tyr	Ser	Phe	Gln	Val	Ala	Arg	Gly	Met	65	70	75	
	Glu	Phe	Leu	Ala	Ser	Arg	Lys	Cys	Ile	His	Arg	Asp	Leu	Ala	Ala	80	85	90	
	Arg	Asn	Ile	Leu	Leu	Ser	Glu	Ser	Asp	Val	Val	Lys	Ile	Cys	Asp	95	100	105	
20	Phe	Gly	Leu	Ala	Arg	Asp	Ile	Tyr	Lys	Asp	Pro	Asp	Tyr	Val	Arg	110	115	120	
	Lys	Gly	Ser	Ala	Arg	Leu	Pro	Leu	Lys	Trp	Met	Ala	Pro	Glu	Ser	125	130	135	
25	Ile	Phe	Asp	Lys	Val	Tyr	Thr	Thr	Gln	Ser	Asp	Val	Trp	Ser	Phe	140	145	150	
	Gly	Val	Leu	Leu	Trp	Glu	Ile	Phe	Ser	Leu	Gly	Ala	Ser	Pro	Tyr	155	160	165	
	Pro	Gly	Val	Gln	Ile	Asn	Glu	Glu	Phe	Cys	Gln	Arg	Leu	Arg	Asp	170	175	180	
30	Gly	Thr	Arg	Met	Arg	Ala	Pro	Glu	Leu	Ala	Thr	Pro	Ala	Ile	Arg	185	190	195	
	Arg	Ile	Met	Leu	Asn	Cys	Trp	Ser	Gly	Asp	Pro	Lys	Ala	Arg	Pro	200	205	210	
35	Ala	Phe	Ser	Glu	Leu	Val	Glu	Ile	Leu	Gly	Asp	Leu	Leu	Gln	Gly	215	220	225	
	Arg	Gly	Leu	Gln	Glu	Glu	Glu	Glu	Val	Cys	Met	Ala	Pro	Arg	Ser	230	235	240	
	Ser	Gln	Ser	Ser	Glu	Glu	Gly	Ser	Phe	Ser	Gln	Val	Ser	Thr	Met	245	250	255	

Ala Leu His Ile Ala Gln Ala Asp Ala Glu Asp Ser Pro Pro Ser
260 265 270

Leu Gln Arg His Ser Leu Ala Ala Arg Tyr Tyr Asn Trp Val Ser
275 280 285

5 Phe Pro Gly Cys Leu Ala Arg Gly Ala Glu Thr Arg Gly Ser Ser
290 295 300

Arg Met Lys Thr Phe Glu Glu Phe Pro Met Thr Pro Thr Thr Tyr
305 310 315

10 Lys Gly Ser Val Asp Asn Gln Thr Asp Ser Gly Met Val Leu Ala
320 325 330

Ser Glu Glu Cys Glu Gln Ile Glu Ser Arg Tyr Arg Gln Glu Ser
335 340 345

Gly Phe Arg
348

15 (2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 7607 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
20 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

TTCGAGCTCG CCCGACATTG ATTATTGACT AGTTATTAAT AGTAATCAAT 50

TACGGGGTCA TTAGTTCATA GCCCATATAT GGAGTTCGCG GTTACATAAC 100

TTACGGTAAA TGGCCCGCCT GGCTGACCGC CCAACGACCC CCGCCCATTG 150

25 ACGTCAATAA TGACGTATGT TCCCATAGTA ACGCCAATAG GGACTTTCCA 200

TTGACGTCAA TGGGTGGAGT ATTTACGGTA AACTGCCCAC TTGGCAGTAC 250

ATCAAGTGTA TCATATGCCA AGTACGCCCC CTATTGACGT CAATGACGGT 300

AAATGGCCCG CCTGGCATTG TGCCAGTAC ATGACCTTAT GGGACTTTCC 350

TACTTGGCAG TACATCTACG TATTAGTCAT CGCTATTACC ATGGTGATGC 400

30 GGTTTTGGCA GTACATCAAT GGGCGTGGAT AGCGGTTTGA CTCACGGGGA 450

TTTCCAAGTC TCCACCCCAT TGACGTCAAT GGGAGTTTGT TTTGGCACCA 500

AAATCAACGG GACTTTCCAA AATGTCGTAA CAACTCCGCC CCATTGACGC 550

AAATGGGCGG TAGGCGTGTA CGGTGGGAGG TCTATATAAG CAGAGCTCGT 600

TTAGTGAACC GTCAGATCGC CTGGAGACGC CATCCACGCT GTTTTGACCT 650

5 CCATAGAAGA CACCGGGACC GATCCAGCCT CCGCGGCCGG GAACGGTGCA 700

TTGGAACGCG GATTCCCCGT GCCAAGAGTG ACGTAAGTAC CGCCTATAGA 750

GTCTATAGGC CCACTTGGCT TCGTTAGAAC GCGGCTACAA TTAATACATA 800

ACCTTATGTA TCATACACAT ACGATTTAGG TGACACTATA GAATAACATC 850

CACTTTGCCT TTCTCTCCAC AGGTGTCCAC TCCCAGGTCC AACTGCACCT 900

10 CGGTTCTATC GATTGAATTC CCCGGGGATC CTCTAGAGAT CCCTCGACCT 950

CGAGTCGACT TTTTTTTTTT TTTTGTAGG CCAAAGGGTA CTTCTTTTTC 1000

TTTATTAATT ACTCAGAAGT CTAGGCCACA GCAATCTACT GTTCTCCTCT 1050

CATTTTCCTA AACTATTTTG ATACCTATTT CTCAGACTTT ATGGGCTATT 1100

AGACATTTCT CACATTTCCA TAGATAATAA CTCATCCGTT TTGCAACCTG 1150

15 ATTCTCAATA TTAAGAGATT AAAACTAATG TATATGACTC TCAGTTGACA 1200

CATACTGAAG TACAGAAAAA TTCCATCATT TCCTTCTGCA AAATGAAAAA 1250

GACTTCGTTT TCTCAACAGC TGCATCATTT TTTTATGCAT AGAAAAAAT 1300

GTGCAATTAC TCCAAGTACA ATCAAGTCAT TTAACATGGC TTTACCATCA 1350

TTGTAGTTAC AGGATATTTT AAAAGAGAAA AAAAAATCTC AAAGCACAGG 1400

TCCTGCTGTG CAGCAAAGCA ATCAAATTCC TTCATAATAA CAGCCTGATG 1450

GGATTGAGCA ATCTGAGGAA TAATGAATAA CCACTCTAAT CAGTAAACAG 1500

GAAAATGCTA CAACAGTCAC TGAGTAAAAA TTGGACTATC ATCTGTTGAT 1550

TCTCTTGATC GACATTTCAA ACAATAAATG GAAATGTAAG TATCTCTTAA 1600

5 AAAGAAAAAT AACTTGGTTT AGTGTGCTTA ATTTTACCAG GCAGTGAGGA 1650

AATTATATAT CACCTTGACT GTCCTGCAGT GTTGCCAGT CAATAAAATG 1700

CACAAATAAT CTTTTTCATA ATACATGGCC AACTTTATCC TATCACTTGA 1750

ATATGTCAGG ATAAACTGAT TGTGCAGTTG GTTGATAACA TTGTATTTTG 1800

GAATGGATTA TTGAATTG TTTTGCTACT TTATTATTTG ATATTCTTCT 1850

10 CCAGTGTTCA TCTTATGAAG TTATTTGCAT CTGAATATGA AGAGTCTGTT 1900

TCAAAATAGT CTTCAAGTTT CCAACGCAGT GTCTCAAATG TAGGTCGTTT 1950

CTTAGGCTCT GCATTCCAGC ACTCCAACAT GATGTTGTAA AATTGCTGTG 2000

GACAGTTGGA TGGTTGCGGA AGTCTATAGT TTTGAGCCAA CATCTGGATT 2050

ACCTGGGCAC CTGTCATACC ACTGTAAGGC ATTTTGCCAT AAGTAATGAT 2100

15 TTCATAAAGA AGGATTCCAA ATGACCATAC ATCGGACTTA ATGCTGAATT 2150

TATTACTACG AATGGCTTCG GCGCAGTCC ACTTCACCGG CAGCTTTATT 2200

TCGTGTCTAG ATTCATAGAT GTCTTCATTA TCTACCTTAA AAACCTGCGC 2250

AAGTCCAAAA TCTGCTACTT TGTAGATATT ATGTTACCA ACGAGGACAT 2300

TTCTGGCAGC CAGATCTCTG TGAATGTAGT TCCGAGACTC CAGATAGGCC 2350

ATTCCAGAGG CAACCTGTGC CGCCATGTCT ACCTGTTGAG TCAGATGGAT 2400

TTTTGATCCA GTGTCATTTT GGAGATATTC TTGCAGACTT CCATGTCTCA 2450

TCAACTCTGT AATAATATAA ATTGGATCTT CTAAAGTGCA AACAGCATAA 2500

AGCTGGATAA GCTTTGGATG TCTTAGGTTC TTCATTATCT GTGCCTCCCT 2550

5 CAGGAAGTCA TTTGGATCCA TTGAACCTGG TTTTAATGTT TTCACTGCTA 2600

CTGGAGTGGT ATTGTTCCAC AGACCTTCCC ATACTTCGCC AACTGACCA 2650

GATCCCAATC GCTTCAGAAG CTGTATGGAG TTGCGGTCTA TCTCCCATTG 2700

GTCCACGTTT TTATACGACA AATCAAATGG AGCTGGGACC TGGATCTTTA 2750

AGCATGGTTT CCCCAGCTTG ACACACAGGC CGTCACTTGT CTTGGTGTAG 2800

10 TGGCTCACAA ATTCGTTTCTG TGTGAAAAG ATTCTTCTTC GCGTGAGAAA 2850

AAATCCCCCT TCATCCAGTC TTTTAATTCT GTAGTGTTTT ACAACTGCTC 2900

CATCTAAAAC TGAAAGAGAG AATTCTCCTT TTTGGCTTTC ACTTTCTCTG 2950

ATTAGAAAGG AACCGGTCTT GTTTTCTGAA TATAATAGTT GTTTCTCTGC 3000

ATCTGATCTT CCGATTGCTC CAAAGAACCA CGGCTCTGCC TGTAGGCTTC 3050

15 TGTCTCAGC CACGTAGTTA GAAGGAATAT AGCCTTGTAG TTGCTGACTG 3100

GAGCCATCTC GTCTTTTCTC CAAGTGCTG GCAAACCACC AGCCCTCATG 3150

CAAAGTGTCC AGAACTTGAA GTTTGTCACC TGCTCGGAAG CTCAAGTCCT 3200

CAGCAGTCCG AGCCTGGTAA TCAAACAAAG CCACAAAGTA GTGGCCATGC 3250

CTCTGTGACT GGGGAGAGCA AAGGGCCCCT GGATTTTCAA TCACGGTTGA 3300

CTTGTCTGCC TCCGTGGACA AACAGGGGAG ATAGGGTTCT AGGTACTCCC 3350

AGAGCCTCTG ACAGATGTTG CTCATTGTGC CTTGGTGGGG AGAAGAGGAG 3400

CAGGGCTTCT CCCTCTCCCC TTAGTCTCTG CGATCCACCT TATCTTCCTT 3450

CACCAGGCAA CTTTGAAGTC AGCACCAACT CACCATACTT CGGAGAGTAT 3500

5 GCAAAGTCCC GTTTCAGATC AGTCCAGCAG CTGGGTTGCA GCAAGTCCTA 3550

CCTGGAGAGA CTTACCGGCT TGCTTTCTGT GGCTGGAGGT GCTACCCCGA 3600

GGCAAACTG AGCAGGAGCT GGGCAGCTGC TCACTAGGAA GGTGTCTTTT 3650

CTTCTTATCT GCTTAAGAAT CCCACAACAA AAATAAAATA AAATTAAAAG 3700

GGCTTTATTT AGACAAATAT CTGAGAACAG AATGGTGCCA TCTTGCCTTT 3750

10 TGTCCCAATA AAAAGTTAGC AAGAGGAAGC TACTAACCCC TGGTAAAACC 3800

TCCACGTCTT GCTTTCGCCA GGGTCGACTC GAGGGATCTT CCATACCTAC 3850

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AATAAAGCAA TAGCATCACA AATTCACAA ATAAAGCATT TTTTCACTG 4000

15 CATCTAGTT GTGGTTTGTC CAAACTCATC AATGTATCTT ATCATGTCTG 4050

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CAGGCTCCCC AGCAGGCAGA AGTATGCAAA GCATGCATCT CAATTAGTCA 4300

GCAACCATAG TCCCGCCCCT AACTCCGCCC ATCCCGCCCC TAACTCCGCC 4350

CAGTTCCGCC CATTCTCCGC CCCATGGCTG ACTAATTTT TTTATTTATG 4400

CAGAGGCCGA GGCCGCCTCG GCCTCTGAGC TATTCCAGAA GTAGTGAGGA 4450

5 GGCTTTTTTG GAGGCCTAGG CTTTGTGAAA AAGCTGTAA CAGCTTGGCA 4500

CTGGCCGTCG TTTTACAACG TCGTGA CTGG GAAAACCCTG GCGTTACCCA 4550

ACTTAATCGC CTTGCAGCAC ATCCCCCTT CGCCAGCTGG CGTAATAGCG 4600

AAGAGGCCCG CACCGATCGC CCTTCCCAAC AGTTGCGCAG CCTGAATGGC 4650

GAATGGCGCC TGATGCGGTA TTTTCTCCTT ACGCATCTGT GCGGTATTTC 4700

10 ACACCGCATA CGTCAAAGCA ACCATAGTAC GCGCCCTGTA GCGGCGCAAT 4750

AAGCGCGGCG GGTGTGGTGG TTACGCGCAG CGTGACCGCT ACACTTGCCA 4800

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CCGATTTAGT GCTTTACGGC ACCTCGACCC CAAAAA ACTT GATTTGGGTG 4950

15 ATGGTTCACG TAGTGGGCCA TCGCCCTGAT AGACGGTTTT TCGCCCTTTG 5000

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AACACTCAAC CCTATCTCGG GCTATTCTTT TGATTTATAA GGGATTTTGC 5100

CGATTTCCGC CTATTGGTTA AAAAATGAGC TGATTTAACA AAAATTTAAC 5150

GCGAATTTTA AAAAAATATT AACGTTTACA ATTTATGGT GCACTCTCAG 5200

TACAACTCTGC TCTGATGCCG CATAGTTAAG CCAGCCCCGA CACCCGCCAA 5250

CACCCGCTGA CGCGCCCTGA CGGGCTTGTC TGCTCCCGGC ATCCGCTTAC 5300

AGACAAGCTG TGACCGTCTC CGGGAGCTGC ATGTGTCAGA GGTTTTCACC 5350

GTCATCACCG AAACGCGCGA GACGAAAGGG CCTCGTGATA CGCCTATTTT 5400

5 TATAGGTAA TGTCATGATA ATAATGGTTT CTTAGACGTC AGGTGGCACT 5450

TTTCGGGGAA ATGTGCGCGG AACCCCTATT TGTTTATTTT TCTAAATACA 5500

TTCAAATATG TATCCGCTCA TGAGACAATA ACCCTGATAA ATGCTTCAAT 5550

AATATTGAAA AAGGAAGAGT ATGAGTATTC AACATTTCCG TGTCGCCCTT 5600

ATTCCCTTTT TTGCGGCATT TTGCCTTCCT GTTTTGTCTC ACCCAGAAAC 5650

10 GCTGGTGAAA GTAAAAGATG CTGAAGATCA GTTGGGTGCA CGAGTGGGTT 5700

ACATCGAACT GGATCTCAAC AGCGGTAAGA TCCTTGAGAG TTTTCGCCCC 5750

GAAGAACGTT TTCCAATGAT GAGCACTTTT AAAGTTCTGC TATGTGGCGC 5800

GGTATTATCC CGTATTGACG CCGGGCAAGA GCAACTCGGT CGCCGCATAC 5850

ACTATTCTCA GAATGACTTG GTTGAGTACT CACCAGTCAC AGAAAAGCAT 5900

15 CTTACGGATG GCATGACAGT AAGAGAATTA TGCAGTGCTG CCATAACCAT 5950

GAGTGATAAC ACTGCGGCCA ACTTACTTCT GACAACGATC GGAGGACCGA 6000

AGGAGCTAAC CGCTTTTTTG CACAACATGG GGGATCATGT AACTCGCCTT 6050

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CACCACGATG CCTGTAGCAA TGGCAACAAC GTTGCGCAAA CTATTAAC TG 6150

GCGAACTACT TACTCTAGCT TCCCGGCAAC AATTAATAGA CTGGATGGAG 6200

GCGGATAAAG TTGCAGGACC ACTTCTGCGC TCGGCCCTTC CGGCTGGCTG 6250

GTTTATTGCT GATAAATCTG GAGCCGGTGA GCGTGGGTCT CGCGGTATCA 6300

TTGCAGCACT GGGGCCAGAT GGTAAGCCCT CCCGTATCGT AGTTATCTAC 6350

5 ACGACGGGGA GTCAGGCAAC TATGGATGAA CGAAATAGAC AGATCGCTGA 6400

GATAGGTGCC TCACTGATTA AGCATTGGTA ACTGTCAGAC CAAGTTTACT 6450

CATATATACT TTAGATTGAT TTAAAACTTC ATTTTAAATT TAAAAGGATC 6500

TAGGTGAAGA TCCTTTTTGA TAATCTCATG ACCAAAATCC CTTAACGTGA 6550

GTTTTCGTTC CACTGAGCGT CAGACCCCGT AGAAAAGATC AAAGGATCTT 6600

10 CTTGAGATCC TTTTTTCTG CGCGTAATCT GCTGCTTGCA AACAAAAAA 6650

CCACCGCTAC CAGCGGTGGT TTGTTTGCCG GATCAAGAGC TACCAACTCT 6700

TTTTCCGAAG GTAAGTGGCT TCAGCAGAGC GCAGATACCA AATACTGTTC 6750

TTCTAGTGTA GCCGTAGTTA GGCCACCACT TCAAGAACTC TGTAGCACCG 6800

CCTACATACC TCGCTCTGCT AATCCTGTTA CCAGTGGCTG CTGCCAGTGG 6850

15 CGATAAGTCG TGTCTTACCG GGTGGACTC AAGACGATAG TTACCGGATA 6900

AGGCGCAGCG GTCGGGCTGA ACGGGGGGTT CGTGACACACA GCCCAGCTTG 6950

GAGCGAACGA CCTACACCGA ACTGAGATAC CTACAGCGTG AGCTATGAGA 7000

AAGCGCCACG CTTCCCGAAG GGAGAAAGGC GGACAGGTAT CCGGTAAGCG 7050

GCAGGGTCGG AACAGGAGAG CGCACGAGGG AGCTTCCAGG GGGAAACGCC 7100

TGGTATCTTT ATAGTCCTGT CGGGTTTCGC CACCTCTGAC TTGAGCGTCG 7150
 ATTTTGTGA TGCTCGTCAG GGGGGCGGAG CCTATGAAA AACGCCAGCA 7200
 ACGCGGCCTT TTTACGGTTC CTGGCCTTTT GCTGGCCTTT TGCTCACATG 7250
 TTCTTCTCTG CGTTATCCCC TGATTCTGTG GATAACCGTA TTACCGCCTT 7300
 5 TGAGTGAGCT GATACCGCTC GCCGCAGCCG AACGACCGAG CGCAGCGAGT 7350
 CAGTGAGCGA GGAAGCGGAA GAGCGCCCAA TACGCAAACC GCCTCTCCCC 7400
 GCGCGTTGGC CGATTCATTA ATGCAGCTGG CACGACAGGT TTCCCGACTG 7450
 GAAAGCGGGC AGTGAGCGCA ACGCAATTAA TGTGAGTTAG CTCACTCATT 7500
 AGGCACCCCA GGCTTTACAC TTTATGCTTC CGGCTCGTAT GTTGTGTGGA 7550
 10 ATTGTGAGCG GATAACAATT TCACACAGGA AACAGCTATG ACATGATTAC 7600
 GAATTAA 7607

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:

- 15 (A) LENGTH: 505 amino acids
 (B) TYPE: amino acid
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

	Met	Ser	Asn	Ile	Cys	Gln	Arg	Leu	Trp	Glu	Tyr	Leu	Glu	Pro	Tyr
	1				5					10					15
20	Leu	Pro	Cys	Leu	Ser	Thr	Glu	Ala	Asp	Lys	Ser	Thr	Val	Ile	Glu
					20					25					30
	Asn	Pro	Gly	Ala	Leu	Cys	Ser	Pro	Gln	Ser	Gln	Arg	His	Gly	His
					35					40					45
25	Tyr	Phe	Val	Ala	Leu	Phe	Asp	Tyr	Gln	Ala	Arg	Thr	Ala	Glu	Asp
					50					55					60
	Leu	Ser	Phe	Arg	Ala	Gly	Asp	Lys	Leu	Gln	Val	Leu	Asp	Thr	Leu
					65					70					75

	His Glu Gly Trp Trp Phe Ala Arg His Leu Glu Lys Arg Arg Asp	80	85	90
	Gly Ser Ser Gln Gln Leu Gln Gly Tyr Ile Pro Ser Asn Tyr Val	95	100	105
5	Ala Glu Asp Arg Ser Leu Gln Ala Glu Pro Trp Phe Phe Gly Ala	110	115	120
	Ile Gly Arg Ser Asp Ala Glu Lys Gln Leu Leu Tyr Ser Glu Asn	125	130	135
10	Lys Thr Gly Ser Phe Leu Ile Arg Glu Ser Glu Ser Gln Lys Gly	140	145	150
	Glu Phe Ser Leu Ser Val Leu Asp Gly Ala Val Val Lys His Tyr	155	160	165
	Arg Ile Lys Arg Leu Asp Glu Gly Gly Phe Phe Leu Thr Arg Arg	170	175	180
15	Arg Ile Phe Ser Thr Leu Asn Glu Phe Val Ser His Tyr Thr Lys	185	190	195
	Thr Ser Asp Gly Leu Cys Val Lys Leu Gly Lys Pro Cys Leu Lys	200	205	210
20	Ile Gln Val Pro Ala Pro Phe Asp Leu Ser Tyr Lys Thr Val Asp	215	220	225
	Gln Trp Glu Ile Asp Arg Asn Ser Ile Gln Leu Leu Lys Arg Leu	230	235	240
	Gly Ser Gly Gln Phe Gly Glu Val Trp Glu Gly Leu Trp Asn Asn	245	250	255
25	Thr Thr Pro Val Ala Val Lys Thr Leu Lys Pro Gly Ser Met Asp	260	265	270
	Pro Asn Asp Phe Leu Arg Glu Ala Gln Ile Met Lys Asn Leu Arg	275	280	285
30	His Pro Lys Leu Ile Gln Leu Tyr Ala Val Cys Thr Leu Glu Asp	290	295	300
	Pro Ile Tyr Ile Ile Thr Glu Leu Met Arg His Gly Ser Leu Gln	305	310	315
	Glu Tyr Leu Gln Asn Asp Thr Gly Ser Lys Ile His Leu Thr Gln	320	325	330
35	Gln Val Asp Met Ala Ala Gln Val Ala Ser Gly Met Ala Tyr Leu	335	340	345
	Glu Ser Arg Asn Tyr Ile His Arg Asp Leu Ala Ala Arg Asn Val	350	355	360

	Leu Val Gly Glu His Asn Ile Tyr Lys Val Ala Asp Phe Gly Leu	
	365	375
	Ala Arg Val Phe Lys Val Asp Asn Glu Asp Ile Tyr Glu Ser Arg	
	380	390
5	His Glu Ile Lys Leu Pro Val Lys Trp Thr Ala Pro Glu Ala Ile	
	395	405
	Arg Ser Asn Lys Phe Ser Ile Lys Ser Asp Val Trp Ser Phe Gly	
	410	420
10	Ile Leu Leu Tyr Glu Ile Ile Thr Tyr Gly Lys Met Pro Tyr Ser	
	425	435
	Gly Met Thr Gly Ala Gln Val Ile Gln Met Leu Ala Gln Asn Tyr	
	440	450
	Arg Leu Pro Gln Pro Ser Asn Cys Pro Gln Gln Phe Tyr Asn Ile	
	455	465
15	Met Leu Glu Cys Trp Asn Ala Glu Pro Lys Glu Arg Pro Thr Phe	
	470	480
	Glu Thr Leu Arg Trp Lys Leu Glu Asp Tyr Phe Glu Thr Asp Ser	
	485	495
20	Ser Tyr Ser Asp Ala Asn Asn Phe Ile Arg	
	500	505

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:

- 25 (A) LENGTH: 404 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

GCGGCCGCAG AGAAAGCAGA GGATGGGGCT TAGCAGCTGG CAGAGCCAGG 50

AGCGGGGAGG TAGCAGAAAG ACCACAAGTA CAAAGAAGTC CTGAAACTTT 100

30 GGTTTTGCTG CTGCAGCCCA TTGAGAGTGA CGACATGGAG CACAAGACCC 150

TGAAGATCAC CGACTTTGGC CTGGCCCGAG AGTGGCACAA AACCACACAA 200

ATGAGTGCCG CNGGCACCTA CNCCTGGATG GCTCCTGAGG TTATCAAGGC 250

CTCCACCTTC TCTAAGGGCA GTGACGTCTG GAGTTTGGG GTGCTGCTGT 300

GGGAACTGCT GACCGGGGAG NTGCCATACC GTGGCATTGA CTGCCTTGCT 350
GTGGCCTATG GCGTAGCTGT TAACAAGCTC AACTGCCAT CCATCCACCT 400
GGCC 404

(2) INFORMATION FOR SEQ ID NO:22:

- 5 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 3120 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
- 10 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:
- ATGAGAGCGT TGGCGCGCGA CGGCGGCCAG CTGCCGCTGC TCGTTGTTTT 50
TTCTGCAATG ATATTGGGA CTATTACAAA TCAAGATCTG CCTGTGATCA 100
AGTGTGTTTT AATCAATCAT AAGAACAATG ATTCATCAGT GGGGAAGTCA 150
TCATCATATC CCATGGTATC AGAATCCCCG GAAGACCTCG GGTGTGCGTT 200
15 GAGACCCCAG AGCTCAGGGA CAGTGACGA AGCTGCCGCT GTGGAAGTGG 250
ATGTATCTGC TTCCATCACA CTGCAAGTGC TGGTCGATGC CCCAGGGAAC 300
ATTTCCTGTC TCTGGGTCTT TAAGCACAGC TCCCTGAATT GCCAGCCACA 350
TTTTGATTTA CAAAACAGAG GAGTTGTTTC CATGGTCATT TTGAAAATGA 400
CAGAAACCCA AGCTGGAGAA TACCTACTTT TTATTGAGAG TGAAGCTACC 450
20 AATTACACAA TATTGTTTAC AGTGAGTATA AGAAATACCC TGCTTTACAC 500
ATTAAGAAGA CCTTACTTTA GAAAAATGGA AAACCAGGAC GCCCTGGTCT 550
GCATATCTGA GAGCGTTCCA GAGCGGATCC TGAATGGGT GCTTTGCGAT 600

TCACAGGGGG AAAGCTGTAA AGAAGAAAGT CCAGCTGTTG TTA AAAAGGA 650

GGAAAAAGTG CTT CATGAAT TATTTGGGAC GGACATAAGG TGCTGTGCCA 700

GAAATGAACT GGGCAGGGAA TGCACCAGGC TGTT CACAAT AGATCTAAAT 750

CAA ACTCCTC AGACCACATT GCCACAATTA TTTCTTAAAG TAGGGGAACC 800

5 CTTATGGATA AGGTGCAAAG CTGTT CATGT GAACCATGGA TTCGGGCTCA 850

CCTGGGAATT AGAAAACAA GCACTCGAGG AGGGCAACTA CTTTGAGATG 900

AGTACCTATT CAACAAACAG AACTATGATA CGGATTCTGT TTGCTTTTGT 950

ATCATCAGTG GCAAGAAACG ACACCGGATA CTACACTTGT TCCTCTTCAA 1000

AGCATCCCAG TCAATCAGCT TTGGTTACCA TCGTAGAAAA GGGATT TATA 1050

10 AATGCTACCA ATTCAAGTGA AGATTATGAA ATTGACCAAT ATGAAGAGTT 1100

TTGTTTTTCT GTCAGGTTTA AAGCCTACCC ACAAATCAGA TGTACGTGGA 1150

CCTTCTCTCG AAAATCATTT CCTTGTGAGC AAAAGGGTCT TGATAACGGA 1200

TACAGCATAT CCAAGTTTTG CAATCATAAG CACCAGCCAG GAGAATATAT 1250

ATTCCATGCA GAAAATGATG ATGCCCAATT TACCAAAATG TTCACGCTGT 1300

15 ATATAAGAAG GAAACCTCAA GTCCTCGCAG AAGCTTCGGC AAGTCAGGCG 1350

TCCTGT TTTCT CGGATGGATA CCCATTACCA TCTTGGACCT GGAAGAAGTG 1400

TTCAGACAAG TCTCCCAACT GCACAGAAGA GATCACAGAA GGAGTCTGGA 1450

ATAGAAAGGC TAACAGAAAA GTGTTTGGAC AGTGGGTGTC GAGCAGTACT 1500

CTAAACATGA GTGAAGCCAT AAAAGGGTTC CTGGTCAAGT GCTGTGCATA 1550

CAATTCCTT GGCACATCTT GTGAGACGAT CCTTTTAAAC TCTCCAGGCC 1600

CCTTCCTTT CATCCAAGAC AACATCTCAT TCTATGCAAC AATTGGTGTT 1650

TGTCTCTCT TCATTGTCGT TTTAACCTG CTAATTTGTC ACAAGTACAA 1700

AAAGCAATTT AGGTATGAAA GCCAGCTACA GATGGTACAG GTGACCGGAT 1750

5 CCTCAGATTA TGAGTACTTC TACGTTGATT TCAGAGAATA TGAATATGAT 1800

GTCAAATGGG AGTTTCCAAG AGAAAATTTA GAGTTTGGGA AGGTACTAGG 1850

ATCAGGTGCT TTTGGAAG TGATGAACGC AACAGCTTAT GGAATTAGCA 1900

AAACAGGAGT CTCAATCCAG GTTACCGTCA AAATGCTGAA AGAAAAAGCA 1950

GACAGCTCTG AAAGAGAGGC ACTCATGTCA GAACTCAAGA TGATGACCCA 2000

10 GCTGGGAAGC CACGAGAATA TTGTGAACCT GCTGGGGGCG TGCACACTGT 2050

CAGGACCAAT TTAATTGATT TTTGAATACT GTTGCTATGG TGATCTTCTC 2100

AACTATCTAA GAAGTAAAAG AGAAAATTT CACAGGACTT GGACAGAGAT 2150

TTTCAAGGAA CACAATTTC GTTTTTACCC CACTTTCCAA TCACATCCAA 2200

ATTCCAGCAT GCCTGGTTCA AGAGAAGTTC AGATACACCC GGACTCGGAT 2250

15 CAAATCTCAG GGCTTCATGG GAATTCATTT CACTCTGAAG ATGAAATTGA 2300

ATATGAAAAC CAAAAAGGC TGAAGAAGA GGAGGACTTG AATGTGCTTA 2350

CATTTGAAGA TCTTCTTTC TTTGCATATC AAGTTGCCAA AGGAATGGAA 2400

TTTCTGGAAT TTAAGTCGTG TGTTCACAGA GACCTGGCCG CCAGGAACGT 2450

GCTTGTCAAC CACGGGAAAG TGGTGAAGAT ATGTGACTTT GGATTGGCTC 2500

GAGATATCAT GAGTGATTCC AACTATGTTG TCAGGGGCAA TGCCCGTCTG 2550
CCTGTAAAAT GGATGGCCCC CGAAAGCCTG TTTGAAGGCA TCTACACCAT 2600
TAAGAGTGAT GTCTGGTCAT ATGGAATATT ACTGTGGGAA ATCTTCTCAC 2650
TTGGTGTGAA TCCTTACCCT GGCATTCCGG TTGATGCTAA CTTCTACAAA 2700
5 CTGATTCAAA ATGGATTAA AATGGATCAG CCATTTTATG CTACAGAAGA 2750
AATATACATT ATAATGCAAT CCTGCTGGGC TTTTGACTCA AGGAAACGGC 2800
CATCCTTCCC TAATTGACT TCGTTTTTAG GATGTCAGCT GGCAGATGCA 2850
GAAGAAGCGA TGTATCAGAA TGTGGATGGC CGTGTTCGG AATGTCCTCA 2900
CACCTACCAA AACAGGCGAC CTTTCAGCAG AGAGATGGAT TTGGGGCTAC 2950
10 TCTCTCCGCA GGCTCAGGTC GAAGATTCGT AGAGGAACAA TTTAGTTTTA 3000
AGGACTTCAT CCCTCCACCT ATCCCTAACA GGCTGTAGAT TACCAAAACA 3050
AGGTTAATTT CATCACTAAA AGAAAATCTA TTATCAACTG CTGCTTCACC 3100
AGACTTTTCT CTAGAGAGCG 3120

(2) INFORMATION FOR SEQ ID NO:23:

- 15 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 3969 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

- 20 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

TCGGCGTCCA CCCGCCAGG GAGAGTCAGA CCTGGGGGGG CGAGGGCCCC 50
CCAAACTCAG TTCGGATCCT ACCCGAGTGA GCGGCGCCA TGGAGCTCCG 100

GGTGCTGCTC TGCTGGGCTT CGTTGGCCGC AGCTTTGGAA GAGACCCTGC 150

TGAACACAAA ATTGGAAACT GCTGATCTGA AGTGGGTGAC ATTCCCTCAG 200

GTGGACGGGC AGTGGGAGGA ACTGAGCGGC CTGGATGAGG AACAGCACAG 250

CGTGCGCACC TACGAAGTGT GTGACGTGCA GCGTGCCCCG GGCCAGGCCC 300

5 ACTGGCTTCG CACAGGTTGG GTCCACGGC GGGGCGCCGT CCACGTGTAC 350

GCCACGCTGC GCTTCACCAT GCTCGAGTGC CTGTCCCTGC CTCGGGCTGG 400

GCGCTCCTGC AAGGAGACCT TCACCGTCTT CTACTATGAG AGCGATGCGG 450

ACACGGCCAC GGCCCTCAG CCAGCCTGGA TGGAGAACCC CTACATCAAG 500

GTGGACACGG TGGCCGCGGA GCATCTCACC CGGAAGCGCC CTGGGGCCGA 550

10 GGCCACCGGG AAGGTGAATG TCAAGACGCT GCGTCTGGGA CCGCTCAGCA 600

AGGCTGGCTT CTACCTGGCC TTCCAGGACC AGGGTGCCTG CATGGCCCTG 650

CTATCCCTGC ACCTCTTCTA CAAAAAGTGC GCCCAGCTGA CTGTGAACCT 700

GACTCGATTG CCGGAGACTG TGCTCGGGA GCTGGTTGTG CCCGTGGCCG 750

GTAGCTGCGT GGTGGATGCC GTCCCCGCCC CTGGCCCCAG CCCCAGCCTC 800

15 TACTGCCGTG AGGATGGCCA GTGGGCCGAA CAGCCGGTCA CGGGCTGCAG 850

CTGTGCTCCG GGGTTCGAGG CAGCTGAGGG GAACACCAAG TGCCGAGCCT 900

GTGCCCAGGG CACCTTCAAG CCCCTGTCAG GAGAAGGGTC CTGCCAGCCA 950

TGCCAGCCA ATAGCCACTC TAACACCATT GGATCAGCCG TCTGCCAGTG 1000

CCGCGTCGGG TACTTCCGGG CACGCACAGA CCCCCGGGT GCACCCTGCA 1050

CCACCCCTCC TTCGGCTCCG CGGAGCGTGG TTTCCCGCCT GAACGGCTCC 1100

TCCCTGCACC TGAATGGAG TGCCCCCTG GAGTCTGGTG GCCGAGAGGA 1150

CCTCACCTAC GCCCTCCGCT GCCGGGAGTG CCGACCCGGA GGCTCCTGTG 1200

CGCCCTGCGG GGGAGACCTG ACTTTTGACC CCGCCCCCGG GGACCTGGTG 1250

5 GAGCCCTGGG TGGTGGTTCG AGGGCTACGT CCTGACTTCA CCTATACCTT 1300

TGAGGTCACT GCATTGAACG GGGTATCCTC CTTAGCCACG GGGCCCGTCC 1350

CATTTGAGCC TGTCAATGTC ACCACTGACC GAGAGGTACC TCCTGCAGTG 1400

TCTGACATCC GGGTGACGCG GTCCTCACCC AGCAGCTTGA GCCTGGCCTG 1450

GGCTGTTCCC CGGGCACCCA GTGGGGCTGT GCTGGACTAC GAGGTCAAAT 1500

10 ACCATGAGAA GGGCGCCGAG GGTCCCAGCA GCGTGCGGTT CCTGAAGACG 1550

TCAGAAAACC GGGCAGAGCT GCGGGGGCTG AAGCGGGGAG CCAGCTACCT 1600

GGTGCAAGTA CGGGCGCGCT CTGAGGCCGG CTACGGGCCC TTCGGCCAGG 1650

AACATCACAG CCAGACCCAA CTGGATGAGA GCGAGGGCTG GCGGGAGCAG 1700

CTGGCCCTGA TTGCGGGCAC GGCAGTCGTG GGTGTGGTCC TGGTCCTGGT 1750

15 GGTCATTGTG GTCGCAGTTC TCTGCCTCAG GAAGCAGAGC AATGGGAGAG 1800

AAGCAGAATA TTCGGACAAA CACGGACAGT ATCTCATCGG ACATGGTACT 1850

AAGGTCTACA TCGACCCCTT CACTTATGAA GACCCTAATG AGGCTGTGAG 1900

GGAAATTTGCA AAAGAGATCG ATGTCTCCTA CGTCAAGATT GAAGAGGTGA 1950

TTGGTGACAG TGAGTTTGGC GAGGTGTGCC GGGGGCGGCT CAAGGCCCCA 2000

GGGAAGAAGG AGAGCTGTGT GGCAATCAAG ACCCTGAAGG GTGGCTACAC 2050

GGAGCGGCAG CGGCGTGAGT TTCTGAGCGA GGCCTCCATC ATGGGCCAGT 2100

TCGAGCACCC CAATATCATC CGCCTGGAGG GCGTGGTCAC CAACAGCATG 2150

CCCGTCATGA TTCTCACAGA GTTCATGGAG AACGGCGCCC TGGACTCCTT 2200

5 CCTGCGGCTA AACGACGGAC AGTTCACAGT CATCCAGCTC GTGGGCATGC 2250

TGCGGGGCAT CGCCTCGGGC ATGCGGTACC TTGCCGAGAT GAGCTACGTC 2300

CACCGAGACC TGGCTGCTCG CAACATCCTA GTCAACAGCA ACCTCGTCTG 2350

CAAAGTGTCT GACTTTGGCC TTTCCCGATT CCTGGAGGAG AACTCTTCCG 2400

ATCCCACCTA CACGAGCTCC CTGGGAGGAA AGATTCCCAT CCGATGGACT 2450

10 GCCCCGAGG CCATTGCCTT CCGGAAGTTC ACTTCGCCA GTGATGCCTG 2500

GAGTTACGGG ATTGTGATGT GGGAGGTGAT GTCATTTGGG GAGAGGCCGT 2550

ACTGGGACAT GAGCAATCAG GACGTGATCA ATGCCATTGA ACAGGACTAC 2600

CGGCTGCCCC CGCCCCAGA CTGTCCCACC TCCCTCCACC AGCTCATGCT 2650

GGACTGTTGG CAGAAAGACC GGAATGCCCC GCCCCGCTTC CCCCAGGTGG 2700

15 TCAGCGCCCT GGACAAGATG ATCCGGAACC CCGCCAGCCT CAAAATCGTG 2750

GCCCCGGAGA ATGGCGGGC CTCACACCCT CTCCTGGACC AGCGGCAGCC 2800

TCACTACTCA GCTTTTGGCT CTGTGGGCGA GTGGCTTCGG GCCATCAAAA 2850

TGGAAGATA CGAAGAAAGT TTCGCAGCCG CTGGCTTTGG CTCCTTCGAG 2900

CTGGTCAGCC AGATCTCTGC TGAGGACCTG CTCCGAATCG GAGTCACTCT 2950

GGCGGGACAC CAGAAGAAAA TCTTGGCCAG TGTCCAGCAC ATGAAGTCCC 3000

AGGCCAAGCC GGGAACCCCG GGTGGGACAG GAGGACCGGC CCCGAGTAC 3050

TGACCTGCAG GAACTCCCCA CCCCAGGGAC ACCGCCTCCC CATTTTCCGG 3100

GGCAGAGTGG GGA CTACAG AGGCCCCCAG CCCTGTGCCC CGCTGGATTG 3150

5 CACTTTGAGC CCGTGGGGTG AGGAGTTGGC AATTTGGAGA GACAGGATTT 3200

GGGGGTTCTG CCATAATAGG AGGGGAAAAT CACCCCCCAG CCACCTCGGG 3250

GAACTCCAGA CCAAGGGTGA GGGCGCCTTT CCCTCAGGAC TGGGTGTGAC 3300

CAGAGGAAAA GGAAGTGCCC AACATCTCCC AGCCTCCCCA GGTGCCCCC 3350

TCACCTTGAT GGGTGCGTTC CCGCAGACCA AAGAGAGTGT GACTCCCTTG 3400

10 CCAGCTCCAG AGTGGGGGGG CTGTCCCAGG GGGCAAGAAG GGGTGTGAGG 3450

GCCCAGTGAC AAAATCATTG GGGTTTGTAG TCCCAACTTG CTGCTGTCAC 3500

CACCAAATC AATCATTTTT TTCCCTTGTA AATGCCCCTC CCCCAGCTGC 3550

TGCCTTCATA TTGAAGGTTT TTGAGTTTGT TTTTGGTCT TAATTTTTCT 3600

CCCCGTTCCC TTTTGTTC TTCGTTTTGT TTTTCTACCG TCCTTGTCAT 3650

15 AACTTTGTGT TGGAGGGAAC CTGTTTCACT ATGGCCTCCT TGCCCAAGT 3700

TGAAACAGGG GCCCATCATC ATGTCTGTTT CCAGAACAGT GCCTTGGTCA 3750

TCCCACATCC CCGGACCCCG CCTGGGACCC CCAAGCTGTG TCCTATGAAG 3800

GGGTGTGGGG TGAGGTAGTG AAAAGGGCGG TAGTTGGTGG TGGAACCCAG 3850

AAACGGACGC CGGTGCTTGG AGGGGTCTT AAATTATATT TAAAAAGTA 3900

ACTTTTGTGA TAAATAAAAG AAAATGGGAC GTGTCCCAGC TCCAGGGGTA 3950

AAAAAAAAAA AAAAAAAAAA 3969

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:

- 5 (A) LENGTH: 1276 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

10	Met	Glu	Leu	Arg	Val	Leu	Leu	Cys	Trp	Ala	Ser	Leu	Ala	Ala	Ala	
	1				5					10					15	
	Leu	Glu	Glu	Thr	Leu	Leu	Asn	Thr	Lys	Leu	Glu	Thr	Ala	Asp	Leu	
					20					25					30	
	Lys	Trp	Val	Thr	Phe	Pro	Gln	Val	Asp	Gly	Gln	Trp	Glu	Glu	Leu	
					35					40					45	
15	Ser	Gly	Leu	Asp	Glu	Gln	His	Ser	Val	Arg	Thr	Tyr	Glu	Val		
					50				55					60		
	Cys	Asp	Val	Gln	Arg	Ala	Pro	Gly	Gln	Ala	His	Trp	Leu	Arg	Thr	
					65				70					75		
20	Gly	Trp	Val	Pro	Arg	Arg	Gly	Ala	Val	His	Val	Tyr	Ala	Thr	Leu	
					80				85					90		
	Arg	Phe	Thr	Met	Leu	Glu	Cys	Leu	Ser	Leu	Pro	Arg	Ala	Gly	Arg	
					95				100					105		
	Ser	Cys	Lys	Glu	Thr	Phe	Thr	Val	Phe	Tyr	Tyr	Glu	Ser	Asp	Ala	
					110				115					120		
25	Asp	Thr	Ala	Thr	Ala	Leu	Thr	Pro	Ala	Trp	Met	Glu	Asn	Pro	Tyr	
					125				130					135		
	Ile	Lys	Val	Asp	Thr	Val	Ala	Ala	Glu	His	Leu	Thr	Arg	Lys	Arg	
					140				145					150		
30	Pro	Gly	Ala	Glu	Ala	Thr	Gly	Lys	Val	Asn	Val	Lys	Thr	Leu	Arg	
					155				160					165		
	Leu	Gly	Pro	Leu	Ser	Lys	Ala	Gly	Phe	Tyr	Leu	Ala	Phe	Gln	Asp	
					170				175					180		
	Gln	Gly	Ala	Cys	Met	Ala	Leu	Leu	Ser	Leu	His	Leu	Phe	Tyr	Lys	
					185				190					195		
35	Lys	Cys	Ala	Gln	Leu	Thr	Val	Asn	Leu	Thr	Arg	Phe	Pro	Glu	Thr	
					200				205					210		

	Val Pro Arg Glu Leu Val Val Pro Val Ala Gly Ser Cys Val Val	215	220	225
	Asp Ala Val Pro Ala Pro Gly Pro Ser Pro Ser Leu Tyr Cys Arg	230	235	240
5	Glu Asp Gly Gln Trp Ala Glu Gln Pro Val Thr Gly Cys Ser Cys	245	250	255
	Ala Pro Gly Phe Glu Ala Ala Glu Gly Asn Thr Lys Cys Arg Ala	260	265	270
10	Cys Ala Gln Gly Thr Phe Lys Pro Leu Ser Gly Glu Gly Ser Cys	275	280	285
	Gln Pro Cys Pro Ala Asn Ser His Ser Asn Thr Ile Gly Ser Ala	290	295	300
	Val Cys Gln Cys Arg Val Gly Tyr Phe Arg Ala Arg Thr Asp Pro	305	310	315
15	Arg Gly Ala Pro Cys Thr Thr Pro Pro Ser Ala Pro Arg Ser Val	320	325	330
	Val Ser Arg Leu Asn Gly Ser Ser Leu His Leu Glu Trp Ser Ala	335	340	345
20	Pro Leu Glu Ser Gly Gly Arg Glu Asp Leu Thr Tyr Ala Leu Arg	350	355	360
	Cys Arg Glu Cys Arg Pro Gly Gly Ser Cys Ala Pro Cys Gly Gly	365	370	375
	Asp Leu Thr Phe Asp Pro Gly Pro Arg Asp Leu Val Glu Pro Trp	380	385	390
25	Val Val Val Arg Gly Leu Arg Pro Asp Phe Thr Tyr Thr Phe Glu	395	400	405
	Val Thr Ala Leu Asn Gly Val Ser Ser Leu Ala Thr Gly Pro Val	410	415	420
30	Pro Phe Glu Pro Val Asn Val Thr Thr Asp Arg Glu Val Pro Pro	425	430	435
	Ala Val Ser Asp Ile Arg Val Thr Arg Ser Ser Pro Ser Ser Leu	440	445	450
	Ser Leu Ala Trp Ala Val Pro Arg Ala Pro Ser Gly Ala Val Leu	455	460	465
35	Asp Tyr Glu Val Lys Tyr His Glu Lys Gly Ala Glu Gly Pro Ser	470	475	480
	Ser Val Arg Phe Leu Lys Thr Ser Glu Asn Arg Ala Glu Leu Arg	485	490	495

	Gly Leu Lys Arg Gly Ala Ser Tyr Leu Val Gln Val Arg Ala Arg	
	500	505 510
	Ser Glu Ala Gly Tyr Gly Pro Phe Gly Gln Glu His His Ser Gln	
	515	520 525
5	Thr Gln Leu Asp Glu Ser Glu Gly Trp Arg Glu Gln Leu Ala Leu	
	530	535 540
	Ile Ala Gly Thr Ala Val Val Gly Val Val Leu Val Leu Val Val	
	545	550 555
10	Ile Val Val Ala Val Leu Cys Leu Arg Lys Gln Ser Asn Gly Arg	
	560	565 570
	Glu Ala Glu Tyr Ser Asp Lys His Gly Gln Tyr Leu Ile Gly His	
	575	580 585
	Gly Thr Lys Val Tyr Ile Asp Pro Phe Thr Tyr Glu Asp Pro Asn	
	590	595 600
15	Glu Ala Val Arg Glu Phe Ala Lys Glu Ile Asp Val Ser Tyr Val	
	605	610 615
	Lys Ile Glu Glu Val Ile Gly Ala Gly Glu Phe Gly Glu Val Cys	
	620	625 630
20	Arg Gly Arg Leu Lys Ala Pro Gly Lys Lys Glu Ser Cys Val Ala	
	635	640 645
	Ile Lys Thr Leu Lys Gly Gly Tyr Thr Glu Arg Gln Arg Arg Glu	
	650	655 660
	Phe Leu Ser Glu Ala Ser Ile Met Gly Gln Phe Glu His Pro Asn	
	665	670 675
25	Ile Ile Arg Leu Glu Gly Val Val Thr Asn Ser Met Pro Val Met	
	680	685 690
	Ile Leu Thr Glu Phe Met Glu Asn Gly Ala Leu Asp Ser Phe Leu	
	695	700 705
30	Arg Leu Asn Asp Gly Gln Phe Thr Val Ile Gln Leu Val Gly Met	
	710	715 720
	Leu Arg Gly Ile Ala Ser Gly Met Arg Tyr Leu Ala Glu Met Ser	
	725	730 735
	Tyr Val His Arg Asp Leu Ala Ala Arg Asn Ile Leu Val Asn Ser	
	740	745 750
35	Asn Leu Val Cys Lys Val Ser Asp Phe Gly Leu Ser Arg Phe Leu	
	755	760 765
	Glu Glu Asn Ser Ser Asp Pro Thr Tyr Thr Ser Ser Leu Gly Gly	
	770	775 780

	Lys	Ile	Pro	Ile	Arg	Trp	Thr	Ala	Pro	Glu	Ala	Ile	Ala	Phe	Arg	785	790	795
	Lys	Phe	Thr	Ser	Ala	Ser	Asp	Ala	Trp	Ser	Tyr	Gly	Ile	Val	Met	800	805	810
5	Trp	Glu	Val	Met	Ser	Phe	Gly	Glu	Arg	Pro	Tyr	Trp	Asp	Met	Ser	815	820	825
	Asn	Gln	Asp	Val	Ile	Asn	Ala	Ile	Glu	Gln	Asp	Tyr	Arg	Leu	Pro	830	835	840
10	Pro	Pro	Pro	Asp	Cys	Pro	Thr	Ser	Leu	His	Gln	Leu	Met	Leu	Asp	845	850	855
	Cys	Trp	Gln	Lys	Asp	Arg	Asn	Ala	Arg	Pro	Arg	Phe	Pro	Gln	Val	860	865	870
	Val	Ser	Ala	Leu	Asp	Lys	Met	Ile	Arg	Asn	Pro	Ala	Ser	Leu	Lys	875	880	885
15	Ile	Val	Ala	Arg	Glu	Asn	Gly	Gly	Ala	Ser	His	Pro	Leu	Leu	Asp	890	895	900
	Gln	Arg	Gln	Pro	His	Tyr	Ser	Ala	Phe	Gly	Ser	Val	Gly	Glu	Trp	905	910	915
20	Leu	Arg	Ala	Ile	Lys	Met	Gly	Arg	Tyr	Glu	Glu	Ser	Phe	Ala	Ala	920	925	930
	Ala	Gly	Phe	Gly	Ser	Phe	Glu	Leu	Val	Ser	Gln	Ile	Ser	Ala	Glu	935	940	945
	Asp	Leu	Leu	Arg	Ile	Gly	Val	Thr	Leu	Ala	Gly	His	Gln	Lys	Lys	950	955	960
25	Ile	Leu	Ala	Ser	Val	Gln	His	Met	Lys	Ser	Gln	Ala	Lys	Pro	Gly	965	970	975
	Thr	Pro	Gly	Gly	Thr	Gly	Gly	Pro	Ala	Pro	Gln	Tyr	Pro	Ala	Gly	980	985	990
30	Thr	Pro	His	Pro	Arg	Asp	Thr	Ala	Ser	Pro	Phe	Ser	Gly	Ala	Glu	995	1000	1005
	Trp	Gly	Leu	Thr	Glu	Ala	Pro	Ser	Pro	Val	Pro	Arg	Trp	Ile	Ala	1010	1015	1020
	Leu	Ala	Arg	Gly	Val	Arg	Ser	Trp	Gln	Phe	Gly	Glu	Thr	Gly	Phe	1025	1030	1035
35	Gly	Gly	Ser	Ala	Ile	Ile	Gly	Gly	Glu	Asn	His	Pro	Pro	Ala	Thr	1040	1045	1050
	Ser	Gly	Asn	Ser	Arg	Pro	Arg	Val	Arg	Ala	Pro	Phe	Pro	Gln	Asp	1055	1060	1065

Ala Arg Asn Ile Leu Val Asn Ser Asn Leu Val Cys Lys Val Ser
1 5 10 15

Asp Phe Gly Leu Ser Arg Phe Leu Glu Asp Asp Thr Ser Asp Pro
 20 25 30
 Thr Tyr Thr Ser Ala Leu Gly Gly Lys Ile Pro Met Arg Trp Thr
 35 40 45
 5 Ala Pro Glu Ala Ile Gln Tyr Arg Lys Phe Ala Ser Ala Ser
 50 55 59

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:

- 10 (A) LENGTH: 54 amino acids
 (B) TYPE: amino acid
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

Asn Val Leu Val Lys Ser Pro Asn His Val Lys Ile Thr Asp Phe
 1 5 10 15
 15 Gly Leu Ala Arg Leu Leu Glu Gly Asp Glu Lys Glu Tyr Asn Ala
 20 25 30
 Asp Gly Gly Lys Met Pro Ile Lys Trp Met Ala Leu Glu Cys Ile
 35 40 45
 His Tyr Arg Lys Phe Thr His Gln Ser
 20 50 54

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:

- 25 (A) LENGTH: 54 amino acids
 (B) TYPE: amino acid
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

Asn Cys Met Leu Ala Gly Asp Met Thr Val Cys Val Ala Asp Phe
 1 5 10 15
 30 Gly Leu Ser Trp Lys Ile Tyr Ser Gly Ala Thr Ile Val Arg Gly
 20 25 30
 Cys Ala Ser Lys Leu Pro Val Lys Trp Leu Ala Leu Gly Ser Leu
 35 40 45
 Ala Asp Asn Leu Tyr Thr Val His Ser
 50 54

(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 27 amino acids
 (B) TYPE: amino acid
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

Asn Cys Leu Val Gly Lys Asn Tyr Thr Ile Lys Ile Ala Asp Phe
 1 5 10 15

Gly Met Ser Arg Asn Leu Tyr Ser Gly Asp Tyr Tyr
 5 20 25 27

(2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 58 amino acids
 (B) TYPE: amino acid
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

Thr Arg Asn Ile Leu Val Glu Asn Glu Asn Arg Val Lys Ile Gly
 1 5 10 15

Asp Phe Gly Leu Thr Lys Val Leu Pro Gln Asp Lys Glu Tyr Tyr
 15 20 25 30

Lys Val Lys Glu Pro Gly Glu Ser Pro Ile Phe Trp Tyr Ala Pro
 35 40 45

Glu Ser Leu Thr Glu Ser Leu Phe Ser Val Ala Ser Asp
 50 55 58

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 58 amino acids
 (B) TYPE: amino acid
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

Ala Arg Asn Ile Leu Val Asn Ser Asn Leu Val Cys Lys Val Ser
 1 5 10 15

Asp Phe Gly Met Ser Arg Val Leu Glu Asp Asp Pro Glu Ala Ala
 20 25 30

Tyr Thr Thr Arg Gly Gly Lys Ile Pro Ile Arg Trp Thr Ala Pro
 35 40 45

Glu Ala Ile Ala Tyr Arg Lys Phe Thr Ser Ala Ser Asp
 50 55 58

(2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 4425 bases
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

TCGGGTCGGA CCCACGCGCA GCGGCCGGAG ATGCAGCGGG GCGCCGCGCT 50

GTGCCTGCGA CTGTGGCTCT GCCTGGGACT CCTGGACGGC CTGGTGAGTG 100

GCTACTCCAT GACCCCCCG ACCTTGAACA TCACGGAGGA GTCACACGTC 150

5 ATCGACACCG GTGACAGCCT GTCCATCTCC TGCAGGGGAC AGCACCCCCT 200

CGAGTGGGCT TGGCCAGGAG CTCAGGAGGC GCCAGCCACC GGAGACAAGG 250

ACAGCGAGGA CACGGGGGTG GTGCGAGACT GCGAGGGCAC AGACGCCAGG 300

CCCTACTGCA AGGTGTTGCT GCTGCACGAG GTACATGCCA ACGACACAGG 350

CAGCTACGTC TGCTACTACA AGTACATCAA GGCACGCATC GAGGGCACCA 400

10 CGGCCGCCAG CTCCTACGTG TTCGTGAGAG ACTTTGAGCA GCCATTCATC 450

AACAAGCCTG ACACGCTCTT GGTCAACAGG AAGGACGCCA TGTGGGTGCC 500

CTGTCTGGTG TCCATCCCCG GCCTCAATGT CACGCTGCGC TCGCAAAGCT 550

CGGTGCTGTG GCCAGACGGG CAGGAGGTGG TGTGGGATGA CCGGCGGGGC 600

ATGCTCGTGT CCACGCCACT GCTGCACGAT GCCCTGTACC TGCAGTGCGA 650

15 GACCACCTGG GGAGACCAGG ACTTCCTTTC CAACCCCTTC CTGGTGCA 700

TCACAGGCAA CGAGCTCTAT GACATCCAGC TGTGCCCAG GAAGTCGCTG 750

GAGCTGCTGG TAGGGGAGAA GCTGGTCCTG AACTGCACCG TGTGGGCTGA 800

GTTTAACTCA GGTGTCACCT TTGACTGGGA CTACCCAGGG AAGCAGGCAG 850

AGCGGGGTAA GTGGGTGCCC GAGCGACGCT CCCAGCAGAC CCACACAGAA 900

CTCTCCAGCA TCCTGACCAT CCACAACGTC AGCCAGCACG ACCTGGGCTC 950

GTATGTGTGC AAGGCCAACA ACGGCATCCA GCGATTTCGG GAGAGCACCG 1000

AGGTCATTGT GCATGAAAAT CCCTTCATCA GCGTCGAGTG GCTCAAAGGA 1050

CCCATCCTGG AGGCCACGGC AGGAGACGAG CTGGTGAAGC TGCCCGTGAA 1100

5 GCTGGCAGCG TACCCCCCGC CCGAGTTCCA GTGGTACAAG GATGGAAAGG 1150

CACTGTCCGG GCGCCACAGT CCACATGCCC TGGTGCTCAA GGAGGTGACA 1200

GAGGCCAGCA CAGGCACCTA CACCCTCGCC CTGTGGA ACT CCGCTGCTGG 1250

CCTGAGGCGC AACATCAGCC TGGAGCTGGT GGTGAATGTG CCCCCCAGA 1300

TACATGAGAA GGAGGCCTCC TCCCCAGCA TCTACTCGCG TCACAGCCGC 1350

10 CAGGCCCTCA CCTGCACGGC CTACGGGGTG CCCCTGCCTC TCAGCATCCA 1400

GTGGCACTGG CGGCCCTGGA CACCCTGCAA GATGTTTGCC CAGCGTAGTC 1450

TCCGGCGGCG GCAGCAGCAA GACCTCATGC CACAGTGCCG TGA CTGGAGG 1500

GCGGTGACCA CGCAGGATGC CGTGAACCCC ATCGAGAGCC TGGACACCTG 1550

GACCGAGTTT GTGGAGGGAA AGAATAAGAC TGTGAGCAAG CTGGTGATCC 1600

15 AGAATGCCAA CGTGTCTGCC ATGTACAAGT GTGTGGTCTC CAACAAGGTG 1650

GGCCAGGATG AGCGGCTCAT CTACTTCTAT GTGACCACCA TCCCCGACGG 1700

CTTCACCATC GAATCCAAGC CATCCGAGGA GCTACTAGAG GGCCAGCCGG 1750

TGCTCCTGAG CTGCCAAGCC GACAGCTACA AGTACGAGCA TCTGCGCTGG 1800

TACCGCCTCA ACCTGTCCAC GCTGCACGAT GCGCACGGGA ACCCGCTTCT 1850

GCTCGACTGC AAGAACGTGC ATCTGTTTCGC CACCCCTCTG GCCGCCAGCC 1900

TGGAGGAGGT GGCACCTGGG GCGCGCCACG CCACGCTCAG CCTGAGTATC 1950

CCCCGCGTCG CGCCCGAGCA CGAGGGCCAC TATGTGTGCG AAGTGCAAGA 2000

CCGGCGCAGC CATGACAAGC ACTGCCACAA GAAGTACCTG TCGGTGCAGG 2050

5 CCCTGGAAGC CCCTCGGCTC ACGCAGAACT TGACCGACCT CCTGGTGAAC 2100

GTGAGCGACT CGCTGGAGAT GCAGTGCTTG GTGGCCGGAG CGCACGCGCC 2150

CAGCATCGTG TGGTACAAAG ACGAGAGGCT GCTGGAGGAA AAGTCTGGAG 2200

TCGACTTGGC GGACTCCAAC CAGAAGCTGA GCATCCAGCG CGTGCGCGAG 2250

GAGGATGCGG GACGCTATCT GTGCAGCGTG TGCAACGCCA AGGGCTGCGT 2300

10 CAACTCCTCC GCCAGCGTGG CCGTGGAAGG CTCCGAGGAT AAGGGCAGCA 2350

TGGAGATCGT GATCCTTGTC GGTACCGGCG TCATCGCTGT CTTCTTCTGG 2400

GTCCTCCTCC TCCTCATCTT CTGTAACATG AGGAGGCCGG CCCACGCAGA 2450

CATCAAGACG GGCTACCTGT CCATCATCAT GGACCCCGGG GAGGTGCCTC 2500

TGGAGGAGCA ATGCGAATAC CTGTCCTACG ATGCCAGCCA GTGGAATTC 2550

15 CCCCAGAGC GGCTGCACCT GGGGAGAGTG CTCGGCTACG GCGCCTTCGG 2600

GAAGGTGGTG GAAGCCTCCG CTTTCGGCAT CCACAAGGGC AGCAGCTGTG 2650

ACACCGTGGC CGTGAAAATG CTGAAAGAGG GCGCCACGGC CAGCGAGCAC 2700

CGCGCGCTGA TGTCGGAGCT CAAGATCCTC ATTCACATCG GCAACCACCT 2750

CAACGTGGTC AACCTCCTCG GGGCGTGCAC CAAGCCGCAG GGCCCCCTCA 2800

TGGTGATCGT GGAGTTCTGC AAGTACGGCA ACCTCTCCAA CTTCTGCGC 2850

GCCAAGCGGG ACGCCTTCAG CCCCTGCGCG GAGAAGTCTC CCGAGCAGCG 2900

CGGACGCTTC CGCGCCATGG TGGAGCTCGC CAGGCTGGAT CGGAGGCGGC 2950

CGGGGAGCAG CGACAGGGTC CTCTTCGCGC GGTTCCTGAA GACCGAGGGC 3000

5 GGAGCGAGGC GGGCTTCTCC AGACCAAGAA GCTGAGGACC TGTGGCTGAG 3050

CCCCTGACC ATGGAAGATC TTGTCTGCTA CAGCTTCCAG GTGGCCAGAG 3100

GGATGGAGTT CCTGGCTTCC CGAAAGTGCA TCCACAGAGA CCTGGCTGCT 3150

CGGAACATTC TGCTGTCGGA AAGCGACGTG GTGAAGATCT GTGACTTTGG 3200

CCTTGCCCGG GACATCTACA AAGACCCTGA CTACGTCCGC AAGGGCAGTG 3250

10 CCCGGCTGCC CCTGAAGTGG ATGGCCCCTG AAAGCATCTT CGACAAGGTG 3300

TACACCACGC AGAGTGACGT GTGGTCCTTT GGGGTGCTTC TCTGGGAGAT 3350

CTTCTCTCTG GGGGCCTCCC CGTACCCTGG GGTGCAGATC AATGAGGAGT 3400

TCTGCCAGCG GCTGAGAGAC GGCACAAGGA TGAGGGCCCC GGAGCTGGCC 3450

ACTCCCGCCA TACCCGCAT CATGCTGAAC TGCTGGTCCG GAGACCCCAA 3500

15 GGCAGACCT GCATTCTCGG AGCTGGTGGA GATCCTGGGG GACCTGCTCC 3550

AGGGCAGGGG CCTGCAAGAG GAAGAGGAGG TCTGCATGGC CCCGCGCAGC 3600

TCTCAGAGCT CAGAAGAGGG CAGCTTCTCG CAGGTGTCCA CCATGGCCCT 3650

ACACATCGCC CAGGCTGACG CTGAGGACAG CCCGCCAAGC CTGCAGCGCC 3700

ACAGCCTGGC CGCCAGGTAT TACAACCTGGG TGTCTTTTCC CGGGTGCCTG 3750

GCCAGAGGGG CTGAGACCCG TGGTTCCTCC AGGATGAAGA CATTGAGGA 3800

ATTCCCATG ACCCAACGA CCTACAAAGG CTCTGTGGAC AACCAGACAG 3850

ACAGTGGGAT GGTGCTGGCC TCGGAGGAGT TTGAGCAGAT AGAGAGCAGG 3900

CATAGACAAG AAAGCGGCTT CAGGTAGCTG AAGCAGAGAG AGAGAAGGCA 3950

5 GCATACGTCA GCATTTTCTT CTCTGCACTT ATAAGAAAGA TCAAAGACTT 4000

TAAGACTTTC GCTATTTCTT CTGCTATCTA CTACAACTT CAAAGAGGAA 4050

CCAGGAGGCC AAGAGGAGCA TGAAAGTGA CAAGGAGTGT GACCACTGAA 4100

GCACCACAGG GAGGGGTTAG GCCTCCGGAT GACTGCGGGC AGGCCTGGAT 4150

AATATCCAGC CTCCCACAAG AAGCTGGTGG AGCAGAGTGT TCCCTGACTC 4200

10 CTCCAAGGAA AGGGAGACGC CCTTTCATGG TCTGCTGAGT AACAGGTGCC 4250

TTCCCAGACA CTGGCGTTAC TGCTTGACCA AAGAGCCCTC AAGCGGCCCT 4300

TATGCCAGCG TGACAGAGGG CTCACCTCTT GCCTTCTAGG TCACTTCTCA 4350

CAATGTCCCT TCAGCACCTG ACCCTGTGCC CGCCAGTTAT TCCTTGGTAA 4400

TATGAGTAAT ACATCAAAGA GTAGT 4425

15 (2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 4425 bases
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- 20 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

AGCCCAGCCT GGGTGCGCGT CGCCGGCCTC TACGTCGCCC CGCGGCGCGA 50

CACGGACGCT GACACCGAGA CGGACCCTGA GGACCTGCCG GACCACTCAC 100

CGATGAGGTA CTGGGGGGGC TGGAACTTGT AGTGCCTCCT CAGTGTGCAG 150

TAGCTGTGGC CACTGTCGGA CAGGTAGAGG ACGTCCCCTG TCGTGGGGGA 200

GCTCACCCGA ACCGGTCCTC GAGTCCTCCG CGGTCGGTGG CCTCTGTTCC 250

5 TGTGCTCCT GTGCCCCAC CACGCTCTGA CGTCCCGTG TCTGCGGTCC 300

GGGATGACGT TCCACAACGA CGACGTGCTC CATGTACGGT TGCTGTGTCC 350

GTCGATGCAG ACGATGATGT TCATGTAGTT CCGTGCGTAG CTCCCGTGGT 400

GCCGGCGGTC GAGGATGCAC AAGCACTCTC TGAAACTCGT CGGTAAGTAG 450

TTGTTCCGAC TGTGCGAGAA CCAGTTGTCC TTCCTGCGGT ACACCCACGG 500

10 GACAGACCAC AGGTAGGGGC CGGAGTTACA GTGCGACGCG AGCGTTTCGA 550

GCCACGACAC CGGTCTGCCC GTCCTCCACC ACACCCTACT GGCCGCCCCG 600

TACGAGCACA GGTGCGGTGA CGACGTGCTA CGGGACATGG ACGTCACGCT 650

CTGGTGGACC CCTCTGGTCC TGAAGGAAAG GTTGGGGAAG GACCACGTGT 700

AGTGTCCGTT GCTCGAGATA CTGTAGGTCG ACAACGGGTC CTTCAGCGAC 750

15 CTCGACGACC ATCCCCTCTT CGACCAGGAC TTGACGTGGC ACACCCGACT 800

CAAATTGAGT CCACAGTGA AACTGACCCT GATGGGTCCC TTCGTCCGTC 850

TCGCCCCATT CACCCACGGG CTCGCTGCGA GGGTCGTCTG GGTGTGTCTT 900

GAGAGGTCGT AGGACTGGTA GGTGTTGCAG TCGGTCGTGC TGGACCCGAG 950

CATACACAG TTCCGGTTGT TGCCGTAGGT CGCTAAAGCC CTCTCGTGGC 1000

TCCAGTAACA CGTACTTTTA GGGAAGTAGT CGCAGCTCAC CGAGTTTCCT 1050

GGGTAGGACC TCCGGTGCCG TCCTCTGCTC GACCACTTCG ACGGGCACTT 1100

CGACCGTCGC ATGGGGGGCG GGCTCAAGGT CACCATGTTC CTACCTTTCC 1150

GTGACAGGCC CGCGGTGTCA GGTGTACGGG ACCACGAGTT CCTCCACTGT 1200

5 CTCCGGTCGT GTCCGTGGAT GTGGGAGCGG GACACCTTGA GCGGACGACC 1250

GGA CTCCGCG TTGTAGTCGG ACCTCGACCA CCACTTACAC GGGGGGTCT 1300

ATGTACTCTT CCTCCGAGG AGGGGGTCGT AGATGAGCGC AGTGTGCGCG 1350

GTCCGGGAGT GGACGTGCCG GATGCCCCAC GGGGACGGAG AGTCGTAGGT 1400

CACCGTGACC GCCGGGACCT GTGGGACGTT CTACAAACGG GTCGCATCAG 1450

10 AGGCCGCCGC CGTCGTCGTT CTGGAGTACG GTGTCACGGC ACTGACCTCC 1500

CGCCACTGGT GCGTCCTACG GCACTTGGGG TAGCTCTCGG ACCTGTGGAC 1550

CTGGCTCAAA CACCTCCCTT TCTTATTCTG ACACTCGTTC GACCACTAGG 1600

TCTTACGGTT GCACAGACGG TACATGTTCA CACACCAGAG GTTGTTCAC 1650

CCGGTCCTAC TCGCCGAGTA GATGAAGATA CACTGGTGGT AGGGGCTGCC 1700

15 GAAGTGGTAG CTTAGGTTTCG GTAGGCTCCT CGATGATCTC CCGGTCGGCC 1750

ACGAGGACTC GACGGTTCGG CTGTCGATGT TCATGCTCGT AGACGCGACC 1800

ATGGCGGAGT TGGACAGGTG CGACGTGCTA CGCGTGCCCT TGGGCGAAGA 1850

CGAGCTGACG TTCTTGACG TAGACAAGCG GTGGGGAGAC CGGCGGTCGG 1900

ACCTCCTCCA CCGTGGACCC CGCGCGGTGC GGTGCGAGTC GGA CT CATAG 1950

GGGGCGCAGC GCGGGCTCGT GCTCCCGGTG ATACACACGC TTCACGTTCT 2000

GGCCGCGTCG GTACTGTTCTG TGACGGTGTT CTTTCATGGAC AGCCACGTCC 2050

GGGACCTTCG GGGAGCCGAG TCGTCTTGA ACTGGCTGGA GGACCACTTG 2100

CACTCGCTGA GCGACCTCTA CGTCACGAAC CACCGGCCTC GCGTGC GCGG 2150

5 GTCGTAGCAC ACCATGTTTC TGCTCTCCGA CGACCTCCTT TTCAGACCTC 2200

AGCTGAACCG CCTGAGGTTG GTCTTCGACT CGTAGGTCGC GCACGCGCTC 2250

CTCCTACGCC CTGCGATAGA CACGTCGCAC ACGTTGCGGT TCCCGACGCA 2300

GTTGAGGAGG CGGTCGCACC GGCACCTTCC GAGGCTCCTA TTCCCGTCGT 2350

ACCTCTAGCA CTAGGAACAG CCATGGCCGC AGTAGCGACA GAAGAAGACC 2400

10 CAGGAGGAGG AGGAGTAGAA GACATTGTAC TCCTCCGCC GGGTGC GTCT 2450

GTAGTTCTGC CCGATGGACA GGTAGTAGTA CCTGGGGCCC CTCCACGGAG 2500

ACCTCCTCGT TACGCTTATG GACAGGATGC TACGGTCGGT CACCCTTAAG 2550

GGGGCTCTCG CCGACGTGGA CCCCTCTCAC GAGCCGATGC CGCGGAAGCC 2600

CTTCCACCAC CTTGAGGAGC GAAAGCCGTA GGTGTTCCCG TCGTCGACAC 2650

15 TGTGGCACC GCACTTTTAC GACTTTCTCC CGCGGTGCCG GTCGCTCGTG 2700

GCGCGCGACT ACAGCCTCGA GTTCTAGGAG TAAGTGTAGC CGTTGGTGGA 2750

GTTGCACCAG TTGAGGAGC CCCGCACGTG GTTCGGCGTC CCGGGGAGT 2800

ACCACTAGCA CCTCAAGACG TTCATGCCGT TGGAGAGGTT GAAGGACGCG 2850

CGGTTGCCCC TCGGAAGTC GGGGACGCGC CTCTTCAGAG GGCTCGTCGC 2900

GCCTGCGAAG GCGCGGTACC ACCTCGAGCG GTCCGACCTA GCCTCCGCCG 2950

GGCCCTCGTC GCTGTCCCAG GAGAAGCGCG CCAAGAGCTT CTGGCTCCCG 3000

CCTCGCTCCG CCCGAAGAGG TCTGGTTCTT CGACTCCTGG ACACCGACTC 3050

GGGCGACTGG TACCTTCTAG AACAGACGAT GTCGAAGGTC CACCGGTCTC 3100

5 CCTACCTCAA GGACCGAAGG GCTTTCACGT AGGTGTCTCT GGACCGACGA 3150

GCCTTGTAAG ACGACAGCCT TTCGCTGCAC CACTTCTAGA CACTGAAACC 3200

GGAACGGGCC CTGTAGATGT TTCTGGGACT GATGCAGGCG TTCCCGTCAC 3250

GGGCCGACGG GGACTTCACC TACCGGGGAC TTTCGTAGAA GCTGTTCCAC 3300

ATGTGGTGCG TCTCACTGCA CACCAGGAAA CCCCACGAAG AGACCCTCTA 3350

10 GAAGAGAGAC CCCCAGAGGG GCATGGGACC CCACGTCTAG TTACTCCTCA 3400

AGACGGTCGC CGACTCTCTG CCGTGTTCCT ACTCCCGGGG CCTCGACCGG 3450

TGAGGGCGGT ATGCGGCGTA GTACGACTTG ACGACCAGGC CTCTGGGGTT 3500

CCGCTCTGGA CGTAAGAGCC TCGACCACCT CTAGGACCCC CTGGACGAGG 3550

TCCCGTCCCC GGACGTTCTC CTTCTCCTCC AGACGTACCG GGGCGCGTCG 3600

15 AGAGTCTCGA GTCTTCTCCC GTCGAAGAGC GTCCACAGGT GGTACCGGGA 3650

TGTGTAGCGG GTCCGACTGC GACTCCTGTC GGGCGGTTCTG GACGTCGCGG 3700

TGTCGGACCG GCGGTCCATA ATGTTGACCC ACAGGAAAGG GCCCACGGAC 3750

CGGTCTCCCC GACTCTGGGC ACCAAGGAGG TCCTACTTCT GTAAACTCCT 3800

TAAGGGGTAC TGGGGTTGCT GGATGTTTCC GAGACACCTG TTGGTCTGTC 3850

TGTCAACCTA CCACGACCGG AGCCTCCTCA AACTCGTCTA TCTCTCGTCC 3900
 GTATCTGTTC TTTCGCCGAA GTCCATCGAC TTCGTCTCTC TCTCTTCCGT 3950
 CGTATGCAGT CGTAAAAGAA GAGACGTGAA TATTCTTTCT AGTTTCTGAA 4000
 ATTCTGAAAG CGATAAAGAA GACGATAGAT GATGTTTGAA GTTCTCCTT 4050
 5 GGTCTCCCG TTCTCCTCGT ACTTTCACCT GTTCTCACA CTGGTGACTT 4100
 CGTGGTGTCC CTCCCCAATC CGGAGGCCTA CTGACGCCCG TCCGGACCTA 4150
 TTATAGGTCG GAGGGTGTTC TTCGACCACC TCGTCTCACA AGGGACTGAG 4200
 GAGGTTCTTT TCCCTCTGCG GGAAAGTACC AGACGACTCA TTGTCCACGG 4250
 AAGGGTCTGT GACCGCAATG ACGAACTGGT TTCTCGGGAG TTCGCCGGGA 4300
 10 ATACGGTCGC ACTGTCTCCC GAGTGGAGAA CGGAAGATCC AGTGAAGAGT 4350
 GTTACAGGGA AGTCGTGGAC TGGGACACGG GCGGTCAATA AGGAACCATT 4400
 ATACTCATT TGTAGTTTCT CATCA 4425

(2) INFORMATION FOR SEQ ID NO:33:

- (i) SEQUENCE CHARACTERISTICS:
 15 (A) LENGTH: 1298 amino acids
 (B) TYPE: amino acid
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

20	Met	Gln	Arg	Gly	Ala	Ala	Leu	Cys	Leu	Arg	Leu	Trp	Leu	Cys	Leu
	1				5					10					15
	Gly	Leu	Leu	Asp	Gly	Leu	Val	Ser	Gly	Tyr	Ser	Met	Thr	Pro	Pro
				20					25						30
	Thr	Leu	Asn	Ile	Thr	Glu	Glu	Ser	His	Val	Ile	Asp	Thr	Gly	Asp
				35					40						45
25	Ser	Leu	Ser	Ile	Ser	Cys	Arg	Gly	Gln	His	Pro	Leu	Glu	Trp	Ala
				50					55						60

	Trp	Pro	Gly	Ala	Gln	Glu	Ala	Pro	Ala	Thr	Gly	Asp	Lys	Asp	Ser	
					65					70					75	
	Glu	Asp	Thr	Gly	Val	Val	Arg	Asp	Cys	Glu	Gly	Thr	Asp	Ala	Arg	
					80					85					90	
5	Pro	Tyr	Cys	Lys	Val	Leu	Leu	Leu	His	Glu	Val	His	Ala	Asn	Asp	
					95					100					105	
	Thr	Gly	Ser	Tyr	Val	Cys	Tyr	Tyr	Lys	Tyr	Ile	Lys	Ala	Arg	Ile	
					110					115					120	
10	Glu	Gly	Thr	Thr	Ala	Ala	Ser	Ser	Tyr	Val	Phe	Val	Arg	Asp	Phe	
					125					130					135	
	Glu	Gln	Pro	Phe	Ile	Asn	Lys	Pro	Asp	Thr	Leu	Leu	Val	Asn	Arg	
					140					145					150	
	Lys	Asp	Ala	Met	Trp	Val	Pro	Cys	Leu	Val	Ser	Ile	Pro	Gly	Leu	
					155					160					165	
15	Asn	Val	Thr	Leu	Arg	Ser	Gln	Ser	Ser	Val	Leu	Trp	Pro	Asp	Gly	
					170					175					180	
	Gln	Glu	Val	Val	Trp	Asp	Asp	Arg	Arg	Gly	Met	Leu	Val	Ser	Thr	
					185					190					195	
20	Pro	Leu	Leu	His	Asp	Ala	Leu	Tyr	Leu	Gln	Cys	Glu	Thr	Thr	Trp	
					200					205					210	
	Gly	Asp	Gln	Asp	Phe	Leu	Ser	Asn	Pro	Phe	Leu	Val	His	Ile	Thr	
					215					220					225	
	Gly	Asn	Glu	Leu	Tyr	Asp	Ile	Gln	Leu	Leu	Pro	Arg	Lys	Ser	Leu	
					230					235					240	
25	Glu	Leu	Leu	Val	Gly	Glu	Lys	Leu	Val	Leu	Asn	Cys	Thr	Val	Trp	
					245					250					255	
	Ala	Glu	Phe	Asn	Ser	Gly	Val	Thr	Phe	Asp	Trp	Asp	Tyr	Pro	Gly	
					260					265					270	
30	Lys	Gln	Ala	Glu	Arg	Gly	Lys	Trp	Val	Pro	Glu	Arg	Arg	Ser	Gln	
					275					280					285	
	Gln	Thr	His	Thr	Glu	Leu	Ser	Ser	Ile	Leu	Thr	Ile	His	Asn	Val	
					290					295					300	
	Ser	Gln	His	Asp	Leu	Gly	Ser	Tyr	Val	Cys	Lys	Ala	Asn	Asn	Gly	
					305					310					315	
35	Ile	Gln	Arg	Phe	Arg	Glu	Ser	Thr	Glu	Val	Ile	Val	His	Glu	Asn	
					320					325					330	
	Pro	Phe	Ile	Ser	Val	Glu	Trp	Leu	Lys	Gly	Pro	Ile	Leu	Glu	Ala	
					335					340					345	

	Thr	Ala	Gly	Asp	Glu	Leu	Val	Lys	Leu	Pro	Val	Lys	Leu	Ala	Ala	
					350					355					360	
	Tyr	Pro	Pro	Pro	Glu	Phe	Gln	Trp	Tyr	Lys	Asp	Gly	Lys	Ala	Leu	
					365					370					375	
5	Ser	Gly	Arg	His	Ser	Pro	His	Ala	Leu	Val	Leu	Lys	Glu	Val	Thr	
					380					385					390	
	Glu	Ala	Ser	Thr	Gly	Thr	Tyr	Thr	Leu	Ala	Leu	Trp	Asn	Ser	Ala	
					395					400					405	
10	Ala	Gly	Leu	Arg	Arg	Asn	Ile	Ser	Leu	Glu	Leu	Val	Val	Asn	Val	
					410					415					420	
	Pro	Pro	Gln	Ile	His	Glu	Lys	Glu	Ala	Ser	Ser	Pro	Ser	Ile	Tyr	
					425					430					435	
	Ser	Arg	His	Ser	Arg	Gln	Ala	Leu	Thr	Cys	Thr	Ala	Tyr	Gly	Val	
					440					445					450	
15	Pro	Leu	Pro	Leu	Ser	Ile	Gln	Trp	His	Trp	Arg	Pro	Trp	Thr	Pro	
					455					460					465	
	Cys	Lys	Met	Phe	Ala	Gln	Arg	Ser	Leu	Arg	Arg	Arg	Gln	Gln	Gln	
					470					475					480	
20	Asp	Leu	Met	Pro	Gln	Cys	Arg	Asp	Trp	Arg	Ala	Val	Thr	Thr	Gln	
					485					490					495	
	Asp	Ala	Val	Asn	Pro	Ile	Glu	Ser	Leu	Asp	Thr	Trp	Thr	Glu	Phe	
					500					505					510	
	Val	Glu	Gly	Lys	Asn	Lys	Thr	Val	Ser	Lys	Leu	Val	Ile	Gln	Asn	
					515					520					525	
25	Ala	Asn	Val	Ser	Ala	Met	Tyr	Lys	Cys	Val	Val	Ser	Asn	Lys	Val	
					530					535					540	
	Gly	Gln	Asp	Glu	Arg	Leu	Ile	Tyr	Phe	Tyr	Val	Thr	Thr	Ile	Pro	
					545					550					555	
30	Asp	Gly	Phe	Thr	Ile	Glu	Ser	Lys	Pro	Ser	Glu	Glu	Leu	Leu	Glu	
					560					565					570	
	Gly	Gln	Pro	Val	Leu	Leu	Ser	Cys	Gln	Ala	Asp	Ser	Tyr	Lys	Tyr	
					575					580					585	
	Glu	His	Leu	Arg	Trp	Tyr	Arg	Leu	Asn	Leu	Ser	Thr	Leu	His	Asp	
					590					595					600	
35	Ala	His	Gly	Asn	Pro	Leu	Leu	Leu	Asp	Cys	Lys	Asn	Val	His	Leu	
					605					610					615	
	Phe	Ala	Thr	Pro	Leu	Ala	Ala	Ser	Leu	Glu	Glu	Val	Ala	Pro	Gly	
					620					625					630	

	Ala Arg His Ala Thr Leu Ser Leu Ser Ile Pro Arg Val Ala Pro	635	640	645
	Glu His Glu Gly His Tyr Val Cys Glu Val Gln Asp Arg Arg Ser	650	655	660
5	His Asp Lys His Cys His Lys Lys Tyr Leu Ser Val Gln Ala Leu	665	670	675
	Glu Ala Pro Arg Leu Thr Gln Asn Leu Thr Asp Leu Leu Val Asn	680	685	690
10	Val Ser Asp Ser Leu Glu Met Gln Cys Leu Val Ala Gly Ala His	695	700	705
	Ala Pro Ser Ile Val Trp Tyr Lys Asp Glu Arg Leu Leu Glu Glu	710	715	720
	Lys Ser Gly Val Asp Leu Ala Asp Ser Asn Gln Lys Leu Ser Ile	725	730	735
15	Gln Arg Val Arg Glu Glu Asp Ala Gly Arg Tyr Leu Cys Ser Val	740	745	750
	Cys Asn Ala Lys Gly Cys Val Asn Ser Ser Ala Ser Val Ala Val	755	760	765
20	Glu Gly Ser Glu Asp Lys Gly Ser Met Glu Ile Val Ile Leu Val	770	775	780
	Gly Thr Gly Val Ile Ala Val Phe Phe Trp Val Leu Leu Leu Leu	785	790	795
	Ile Phe Cys Asn Met Arg Arg Pro Ala His Ala Asp Ile Lys Thr	800	805	810
25	Gly Tyr Leu Ser Ile Ile Met Asp Pro Gly Glu Val Pro Leu Glu	815	820	825
	Glu Gln Cys Glu Tyr Leu Ser Tyr Asp Ala Ser Gln Trp Glu Phe	830	835	840
30	Pro Arg Glu Arg Leu His Leu Gly Arg Val Leu Gly Tyr Gly Ala	845	850	855
	Phe Gly Lys Val Val Glu Ala Ser Ala Phe Gly Ile His Lys Gly	860	865	870
	Ser Ser Cys Asp Thr Val Ala Val Lys Met Leu Lys Glu Gly Ala	875	880	885
35	Thr Ala Ser Glu His Arg Ala Leu Met Ser Glu Leu Lys Ile Leu	890	895	900
	Ile His Ile Gly Asn His Leu Asn Val Val Asn Leu Leu Gly Ala	905	910	915

	Cys Thr Lys Pro Gln Gly Pro Leu Met Val Ile Val Glu Phe Cys	920	925	930
	Lys Tyr Gly Asn Leu Ser Asn Phe Leu Arg Ala Lys Arg Asp Ala	935	940	945
5	Phe Ser Pro Cys Ala Glu Lys Ser Pro Glu Gln Arg Gly Arg Phe	950	955	960
	Arg Ala Met Val Glu Leu Ala Arg Leu Asp Arg Arg Arg Pro Gly	965	970	975
10	Ser Ser Asp Arg Val Leu Phe Ala Arg Phe Ser Lys Thr Glu Gly	980	985	990
	Gly Ala Arg Arg Ala Ser Pro Asp Gln Glu Ala Glu Asp Leu Trp	995	1000	1005
	Leu Ser Pro Leu Thr Met Glu Asp Leu Val Cys Tyr Ser Phe Gln	1010	1015	1020
15	Val Ala Arg Gly Met Glu Phe Leu Ala Ser Arg Lys Cys Ile His	1025	1030	1035
	Arg Asp Leu Ala Ala Arg Asn Ile Leu Leu Ser Glu Ser Asp Val	1040	1045	1050
20	Val Lys Ile Cys Asp Phe Gly Leu Ala Arg Asp Ile Tyr Lys Asp	1055	1060	1065
	Pro Asp Tyr Val Arg Lys Gly Ser Ala Arg Leu Pro Leu Lys Trp	1070	1075	1080
	Met Ala Pro Glu Ser Ile Phe Asp Lys Val Tyr Thr Thr Gln Ser	1085	1090	1095
25	Asp Val Trp Ser Phe Gly Val Leu Leu Trp Glu Ile Phe Ser Leu	1100	1105	1110
	Gly Ala Ser Pro Tyr Pro Gly Val Gln Ile Asn Glu Glu Phe Cys	1115	1120	1125
30	Gln Arg Leu Arg Asp Gly Thr Arg Met Arg Ala Pro Glu Leu Ala	1130	1135	1140
	Thr Pro Ala Ile Arg Arg Ile Met Leu Asn Cys Trp Ser Gly Asp	1145	1150	1155
	Pro Lys Ala Arg Pro Ala Phe Ser Glu Leu Val Glu Ile Leu Gly	1160	1165	1170
35	Asp Leu Leu Gln Gly Arg Gly Leu Gln Glu Glu Glu Val Cys	1175	1180	1185
	Met Ala Pro Arg Ser Ser Gln Ser Ser Glu Glu Gly Ser Phe Ser	1190	1195	1200

Gln Val Ser Thr Met Ala Leu His Ile Ala Gln Ala Asp Ala Glu
1205 1210 1215

Asp Ser Pro Pro Ser Leu Gln Arg His Ser Leu Ala Ala Arg Tyr
1220 1225 1230

5 Tyr Asn Trp Val Ser Phe Pro Gly Cys Leu Ala Arg Gly Ala Glu
1235 1240 1245

Thr Arg Gly Ser Ser Arg Met Lys Thr Phe Glu Glu Phe Pro Met
1250 1255 1260

10 Thr Pro Thr Thr Tyr Lys Gly Ser Val Asp Asn Gln Thr Asp Ser
1265 1270 1275

Gly Met Val Leu Ala Ser Glu Glu Phe Glu Gln Ile Glu Ser Arg
1280 1285 1290

His Arg Gln Glu Ser Gly Phe Arg
1295 1298

15 (2) INFORMATION FOR SEQ ID NO:34:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 3348 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
20 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

ATGGCTGGGA TTTTCTATTT CGCCCTATTT TCGTGTCTCT TCGGGATTG 50

CGACGCTGTC ACAGGTTCCA GGGTATACCC CGCGAATGAA GTTACCTTAT 100

TGGATTCCAG ATCTGTTCAG GGAGAACTTG GGTGGATAGC AAGCCCTCTG 150

25 GAAGGAGGGT GGGAGGAAGT GAGTATCATG GATGAAAAA ATACACCAAT 200

CCGAACCTAC CAAGTGTGCA ATGTGATGGA ACCCAGCCAG AATAACTGGC 250

TACGAACTGA TTGGATCACC CGAGAAGGGG CTCAGAGGGT GTATATTGAG 300

ATTAAATTCA CCTTGAGGGA CTGCAATAGT CTTCGGGCG TCATGGGGAC 350

TTGCAAGGAG ACGTTTAACC TGTACTACTA TGAATCAGAC AACGACAAAG 400

30 AGCGTTTCAT CAGAGAGAAC CAGTTTGTCA AAATTGACAC CATTGCTGCT 450

GATGAGAGCT TCACCCAAGT GGACATTGGT GACAGAATCA TGAAGCTGAA 500

CACCGAGATC CGGGATGTAG GGCCATTAAG CAAAAAGGGG TTTTACCTGG 550

CTTTTCAGGA TGTGGGGGCC TGCATCGCCC TGGTATCAGT CCGTGTGTTC 600

TATAAAAAGT GTCCACTCAC AGTCCGCAAT CTGGCCCAGT TTCCTGACAC 650

5 CATCACAGGG GCTGATACGT CTTCCCTGGT GGAAGTTCGA GGCTCCTGTG 700

TCAACAATC AGAAGAGAAA GATGTGCCAA AAATGTACTG TGGGGCAGAT 750

GGTGAATGGC TGGTACCCAT TGGCAACTGC CTATGCAACG CTGGGCATGA 800

GGAGCGGAGC GGAGAATGCC AAGCTTGCAA AATTGGATAT TACAAGGCTC 850

TCTCCACGGA TGCCACCTGT GCCAAGTGCC CACCCACAG CTA CTCTGTC 900

10 TGGGAAGGAG CCACCTCGTG CACCTGTGAC CGAGGCTTTT TCAGAGCTGA 950

CAACGATGCT GCCTCTATGC CCTGCACCCG TCCACCATCT GCTCCCCTGA 1000

ACTTGATTTC AAATGTCAAC GAGACATCTG TGAAGTTGGA ATGGAGTAGC 1050

CCTCAGAATA CAGGTGGCCG CCAGGACATT TCCTATAATG TGGTATGCAA 1100

GAAATGTGGA GCTGGTGACC CCAGCAAGTG CCGACCCTGT GGAAGTGGGG 1150

15 TCCACTACAC CCCACAGCAG AATGGCTTGA AGACCACCAA AGGCTCCATC 1200

ACTGACCTCC TAGCTCATAC CAATTACACC TTTGAAATCT GGGCTGTGAA 1250

TGGAGTGTCC AAATATAACC CTAACCCAGA CCAATCAGTT TCTGTCACTG 1300

TGACCACCAA CCAAGCAGCA CCATCATCCA TTGCTTTGGT CCAGGCTAAA 1350

GAAGTCACAA GATACAGTGT GGCCTGGCT TGGCTGGAAC CAGATCGGCC 1400

CAATGGGGTA ATCCTGGAAT ATGAAGTCAA GTATTATGAG AAGGATCAGA 1450

ATGAGCGAAG CTATCGTATA GTTCGGACAG CTGCCAGGAA CACAGATATC 1500

AAAGGCCTGA ACCCTCTCAC TTCCTATGTT TTCCACGTGC GAGCCAGGAC 1550

AGCAGCTGGC TATGGAGACT TCAGTGAGCC CTTGGAGGTT ACAACCAACA 1600

5 CAGTGCCTTC CCGGATCATT GGAGATGGGG CTAAGTCCAC AGTCCTTCTG 1650

GTCTCTGTCT CGGGCAGTGT GGTGCTGGTG GTAATTCTCA TTGCAGCTTT 1700

TGTCATCAGC CGGAGACGGA GTAAATACAG TAAAGCCAAA CAAGAAGCGG 1750

ATGAAGAGAA ACATTTGAAT CAAGGTGTAA GAACATATGT GGACCCCTTT 1800

ACGTACGAAG ATCCCAACCA AGCAGTGC GAAGTTTGCCA AAGAAATTGA 1850

10 CGCATCCTGC ATTAAGATTG AAAAAGTTAT AGGAGTTGGT GAATTTGGTG 1900

AGGTATGCAG TGGGCGTCTC AAAGTGCCTG GCAAGAGAGA GATCTGTGTG 1950

GCTATCAAGA CTCTGAAAGC TGGTTATACA GACAAACAGA GGAGAGACTT 2000

CCTGAGTGAG GCCAGCATCA TGGGACAGTT TGACCATCCG AACATCATT 2050

ACTTGAAGG CGTGGTCACT AAATGTAAAC CAGTAATGAT CATAACAGAG 2100

15 TACATGGAGA ATGGCTCCTT GGATGCATTC CTCAGGAAAA ATGATGGCAG 2150

ATTACAGTC ATTCAGCTGG TGGGCATGCT TCGTGGCATT GGGTCTGGGA 2200

TGAAGTATTT ATCTGATATG AGCTATGTGC ATCGTGATCT GGCCGCACGG 2250

AACATCCTGG TGAACAGCAA CTTGGTCTGC AAAGTGTCTG ATTTTGGCAT 2300

GTCCCGAGTG CTTGAGGATG ATCCGGAAGC AGCTTACACC ACCAGGGGTG 2350

GCAAGATTCC TATCCGGTGG ACTGCGCCAG AAGCAATTGC CTATCGTAAA 2400

TTCACATCAG CAAGTGATGT ATGGAGCTAT GGAATCGTTA TGTGGGAAGT 2450

GATGTCGTAC GGGGAGAGGC CCTATTGGGA TATGTCCAAT CAAGATGTGA 2500

TTAAAGCCAT TGAGGAAGGC TATCGGTTAC CCCCTCCAAT GGACTGCCCC 2550

5 ATTGCGCTCC ACCAGCTGAT GCTAGACTGC TGGCAGAAGG AGAGGAGCGA 2600

CAGGCCTAAA TTTGGGCAGA TTGTCAACAT GTTGGACAAA CTCATCCGCA 2650

ACCCCAACAG CTTGAAGAGG ACAGGGACGG AGAGCTCCAG ACCTAACACT 2700

GCCTTGTTGG ATCCAAGCTC CCCTGAATTC TCTGCTGTGG TATCAGTGGG 2750

CGATTGGCTC CAGGCCATTA AAATGGACCG GTATAAGGAT AACTTCACAG 2800

10 CTGCTGGTTA TACCACACTA GAGGCTGTGG TGCACGTGAA CCAGGAGGAC 2850

CTGGCAAGAA TTGGTATCAC AGCCATCACA CACCAGAATA AGATTTTGAG 2900

CAGTGTCAG GCAATGCGAA CCCAAATGCA GCAGATGCAC GGCAGAATGG 2950

TTCCCGTCTG AGCCAGTACT GAATAAACTC AAAACTCTTG AAATTAGTTT 3000

ACCTCATCCA TGCACTTTAA TTGAAGAACT GCACTTTTTT TACTTCGTCT 3050

15 TCGCCCTCTG AAATTAAAGA AATGAAAAA AAAAAACAAT ATCTGCAGCG 3100

TTGCTTGGTG CACAGATTGC TGAAACTGTG GGGCTTACAG AAATGACTGC 3150

CGGTCATTTG AATGAGACCT GGAACAAATC GTTCTCAGA AGTACTTTTC 3200

TGTTCATCAC CAGTCTGTAA AATACATGTA CCTATAGAAA TAGAACACTG 3250

CCTCTGAGTT TTGATGCTGT ATTTGCTGCC AGACACTGAG CTTCTGAGAC 3300

ATCCCTGATT CTCTCTCCAT TTGGAATTAC AACGGTCGAC GAGCTCGA 3348

(2) INFORMATION FOR SEQ ID NO:35:

(i) SEQUENCE CHARACTERISTICS:

- 5 (A) LENGTH: 3348 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

TACCGACCCT AAAAGATAAA GCGGGATAAA AGCACAGAGA AGCCCTAAAC 50
10 GCTGCGACAG TGTCCAAGGT CCCATATGGG GCGCTTACTT CAATGGAATA 100
ACCTAAGGTC TAGACAAGTC CCTCTTGAAC CCACCTATCG TTCGGGAGAC 150
CTTCCTCCA CCCTCCTTCA CTCATAGTAC CTACTTTTTT TATGTGGTTA 200
GGCTTGGATG GTTACACAGT TACACTACCT TGGGTCGGTC TTATTGACCG 250
ATGCTTGACT AACCTAGTGG GCTCTTCCCC GAGTCTCCCA CATATAACTC 300
15 TAATTTAAGT GGAAGTCCCT GACGTTATCA GAAGGCCCGC AGTACCCCTG 350
AACGTTCCCTC TGCAAATTGG ACATGATGAT ACTTAGTCTG TTGCTGTTTC 400
TCGCAAAGTA GTCTCTCTTG GTCAAACAGT TTAACTGTG GTAACGACGA 450
CTACTCTCGA AGTGGGTTC A CTGTAACCA CTGTCTTAGT ACTTCGACTT 500
GTGGCTCTAG GCCCTACATC CCGGTAATTC GTTTTTCCCC AAAATGGACC 550
20 GAAAAGTCCT ACACCCCGG ACGTAGCGGG ACCATAGTCA GGCACACAAG 600
ATATTTTCA CAGGTGAGTG TCAGGCGTTA GACCGGGTCA AAGGACTGTG 650
GTAGTGTCCT CGACTATGCA GAAGGGACCA CCTTCAAGCT CCGAGGACAC 700

AGTTGTTGAG TCTTCTCTTT CTACACGGTT TTTACATGAC ACCCCGTCTA 750

CCACTTACCG ACCATGGGTA ACCGTTGACG GATACGTTGC GACCCGTACT 800

CCTCGCCTCG CCTCTTACGG TTCGAACGTT TTAACCTATA ATGTTCCGAG 850

AGAGGTGCCT ACGGTGGACA CGGTTACGG GTGGGGTGTC GATGAGACAG 900

5 ACCCTTCCTC GGTGGAGCAC GTGGACACTG GCTCCGAAAA AGTCTCGACT 950

GTTGCTACGA CGGAGATACG GGACGTGGGC AGGTGGTAGA CGAGGGGACT 1000

TGAACTAAAG TTTACAGTTG CTCTGTAGAC ACTTGAACCT TACCTCATCG 1050

GGAGTCTTAT GTCCACCGGC GGTCTGTAA AGGATATTAC ACCATACGTT 1100

CTTTACACCT CGACCACTGG GGTCTTCAC GGCTGGGACA CCTTCACCCC 1150

10 AGGTGATGTG GGGTGTGTC TTACCGAACT TCTGGTGGTT TCCGAGGTAG 1200

TGACTGGAGG ATCGAGTATG GTTAATGTGG AAACTTTAGA CCCGACACTT 1250

ACCTCACAGG TTTATATTGG GATTGGGTCT GGTTAGTCAA AGACAGTGAC 1300

ACTGGTGGTT GGTTCTCGT GGTAGTAGGT AACGAAACCA GGTCCGATTT 1350

CTTCAGTGTT CTATGTCACA CCGTGACCGA ACCGACCTTG GTCTAGCCGG 1400

15 GTTACCCCAT TAGGACCTTA TACTTCAGTT CATAATACTC TTCCTAGTCT 1450

TACTCGCTTC GATAGCATAT CAAGCCTGTC GACGGTCCTT GTGTCTATAG 1500

TTTCCGGACT TGGGAGAGTG AAGGATACAA AAGGTGCACG CTCGGTCCTG 1550

TCGTCGACCG ATACCTCTGA AGTCACTCGG GAACCTCCAA TGTTGGTTGT 1600

GTCACGGAAG GGCCTAGTAA CCTCTACCCC GATTGAGGTG TCAGGAAGAC 1650

CAGAGACAGA GCCCGTCACA CCACGACCAC CATTAAGAGT AACGTCGAAA 1700

ACAGTAGTCG GCCTCTGCCT CATTTATGTC ATTTCGGTTT GTTCTTCGCC 1750

TACTTCTCTT TGTAAACTTA GTTCCACATT CTTGTATACA CCTGGGGAAA 1800

TGCATGCTTC TAGGGTTGGT TCGTCACGCT CTCAAACGGT TTCTTTAACT 1850

5 GCGTAGGACG TAATTCTAAC TTTTCAATA TCCTCAACCA CTTAAACCAC 1900

TCCATACGTC ACCCGCAGAG TTTCACGGAC CGTTCTCTCT CTAGACACAC 1950

CGATAGTTCT GAGACTTTTCG ACCAATATGT CTGTTTGTCT CCTCTCTGAA 2000

GGACTCACTC CGGTCGTAGT ACCCTGTCAA ACTGGTAGGC TTGTAGTAAG 2050

TGAACCTTCC GCACCAGTGA TTTACATTG GTCATTACTA GTATTGTCTC 2100

10 ATGTACCTCT TACCGAGGAA CCTACGTAAG GAGTCCTTTT TACTACCGTC 2150

TAAATGTCAG TAAGTCGACC ACCCGTACGA AGCACCGTAA CCCAGACCCT 2200

ACTTCATAAA TAGACTATAC TCGATACACG TAGCACTAGA CCGGCGTGCC 2250

TTGTAGGACC ACTTGTCGTT GAACCAGACG TTTCACAGAC TAAAACCGTA 2300

CAGGGCTCAC GAACTCCTAC TAGGCCTTCG TCGAATGTGG TGGTCCCCAC 2350

15 CGTTCTAAGG ATAGGCCACC TGACGCGGTC TTCGTTAACG GATAGCATTT 2400

AAGTGTAGTC GTTCACTACA TACCTCGATA CCTTAGCAAT ACACCCTTCA 2450

CTACAGCATG CCCCTCTCCG GGATAACCCT ATACAGGTTA GTTCTACACT 2500

AATTTGCGTA ACTCCTTCCG ATAGCCAATG GGGGAGGTTA CCTGACGGGG 2550

TAACGCGAGG TGGTCGACTA CGATCTGACG ACCGTCTTCC TCTCCTCGCT 2600

GTCCGGATT AAACCCGTCT AACAGTTGTA CAACCTGTTT GAGTAGGCGT 2650
 TGGGGTTGTC GAACTTCTCC TGTCCCTGCC TCTCGAGGTC TGGATTGTGA 2700
 CGGAACAACC TAGGTTCGAG GGGACTTAAG AGACGACACC ATAGTCACCC 2750
 GCTAACCGAG GTCCGGTAAT TTTACCTGGC CATATTCTTA TTGAAGTGTC 2800
 5 GACGACCAAT ATGGTGTGAT CTCCGACACC ACGTGCACTT GGTCTCCTG 2850
 GACCGTTCTT AACCATAGTG TCGGTAGTGT GTGGTCTTAT TCTAAAACTC 2900
 GTCACAGGTC CGTTACGCTT GGGTTTACGT CGTCTACGTG CCGTCTTACC 2950
 AAGGGCAGAC TCGGTCATGA CTTATTTGAG TTTTGAGAAC TTTAATCAAA 3000
 TGGAGTAGGT ACGTGAAATT AACTTCTTGA CGTGAAAAAA ATGAAGCAGA 3050
 10 AGCGGGAGAC TTTAATTTCT TTACTTTTTT TTTTTTGTTA TAGACGTCGC 3100
 AACGAACCAC GTGTCTAACG ACTTTGACAC CCCGAATGTC TTTACTGACG 3150
 GCCAGTAAAC TTAAGTCTGA CCTTGTCTAG CAAAGAGTCT TCATGAAAAG 3200
 ACAAGTAGTG GTCAGACATT TTATGTACAT GGATATCTTT ATCTTGTGAC 3250
 GGAGACTCAA AACTACGACA TAAACGACGG TCTGTGACTC GAAGACTCTG 3300
 15 TAGGGACTAA GAGAGAGGTA AACCTTAATG TTGCCAGCTG CTCGAGCT 3348

(2) INFORMATION FOR SEQ ID NO:36:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1104 amino acids
 (B) TYPE: amino acid
 20 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

Met Ala Gly Ile Phe Tyr Phe Ala Leu Phe Ser Cys Leu Phe Gly
 1 5 10 15

	Ile Cys Asp Ala Val Thr Gly Ser Arg Val Tyr Pro Ala Asn Glu	
	20	25 30
	Val Thr Leu Leu Asp Ser Arg Ser Val Gln Gly Glu Leu Gly Trp	
	35	40 45
5	Ile Ala Ser Pro Leu Glu Gly Gly Trp Glu Glu Val Ser Ile Met	
	50	55 60
	Asp Glu Lys Asn Thr Pro Ile Arg Thr Tyr Gln Val Cys Asn Val	
	65	70 75
10	Met Glu Pro Ser Gln Asn Asn Trp Leu Arg Thr Asp Trp Ile Thr	
	80	85 90
	Arg Glu Gly Ala Gln Arg Val Tyr Ile Glu Ile Lys Phe Thr Leu	
	95	100 105
	Arg Asp Cys Asn Ser Leu Pro Gly Val Met Gly Thr Cys Lys Glu	
	110	115 120
15	Thr Phe Asn Leu Tyr Tyr Tyr Glu Ser Asp Asn Asp Lys Glu Arg	
	125	130 135
	Phe Ile Arg Glu Asn Gln Phe Val Lys Ile Asp Thr Ile Ala Ala	
	140	145 150
20	Asp Glu Ser Phe Thr Gln Val Asp Ile Gly Asp Arg Ile Met Lys	
	155	160 165
	Leu Asn Thr Glu Ile Arg Asp Val Gly Pro Leu Ser Lys Lys Gly	
	170	175 180
	Phe Tyr Leu Ala Phe Gln Asp Val Gly Ala Cys Ile Ala Leu Val	
	185	190 195
25	Ser Val Arg Val Phe Tyr Lys Lys Cys Pro Leu Thr Val Arg Asn	
	200	205 210
	Leu Ala Gln Phe Pro Asp Thr Ile Thr Gly Ala Asp Thr Ser Ser	
	215	220 225
30	Leu Val Glu Val Arg Gly Ser Cys Val Asn Asn Ser Glu Glu Lys	
	230	235 240
	Asp Val Pro Lys Met Tyr Cys Gly Ala Asp Gly Glu Trp Leu Val	
	245	250 255
	Pro Ile Gly Asn Cys Leu Cys Asn Ala Gly His Glu Glu Arg Ser	
	260	265 270
35	Gly Glu Cys Gln Ala Cys Lys Ile Gly Tyr Tyr Lys Ala Leu Ser	
	275	280 285
	Thr Asp Ala Thr Cys Ala Lys Cys Pro Pro His Ser Tyr Ser Val	
	290	295 300

	Trp	Glu	Gly	Ala	Thr	Ser	Cys	Thr	Cys	Asp	Arg	Gly	Phe	Phe	Arg	
					305					310					315	
	Ala	Asp	Asn	Asp	Ala	Ala	Ser	Met	Pro	Cys	Thr	Arg	Pro	Pro	Ser	
					320					325					330	
5	Ala	Pro	Leu	Asn	Leu	Ile	Ser	Asn	Val	Asn	Glu	Thr	Ser	Val	Asn	
					335					340					345	
	Leu	Glu	Trp	Ser	Ser	Pro	Gln	Asn	Thr	Gly	Gly	Arg	Gln	Asp	Ile	
					350					355					360	
10	Ser	Tyr	Asn	Val	Val	Cys	Lys	Lys	Cys	Gly	Ala	Gly	Asp	Pro	Ser	
					365					370					375	
	Lys	Cys	Arg	Pro	Cys	Gly	Ser	Gly	Val	His	Tyr	Thr	Pro	Gln	Gln	
					380					385					390	
	Asn	Gly	Leu	Lys	Thr	Thr	Lys	Gly	Ser	Ile	Thr	Asp	Leu	Leu	Ala	
					395					400					405	
15	His	Thr	Asn	Tyr	Thr	Phe	Glu	Ile	Trp	Ala	Val	Asn	Gly	Val	Ser	
					410					415					420	
	Lys	Tyr	Asn	Pro	Asn	Pro	Asp	Gln	Ser	Val	Ser	Val	Thr	Val	Thr	
					425					430					435	
20	Thr	Asn	Gln	Ala	Ala	Pro	Ser	Ser	Ile	Ala	Leu	Val	Gln	Ala	Lys	
					440					445					450	
	Glu	Val	Thr	Arg	Tyr	Ser	Val	Ala	Leu	Ala	Trp	Leu	Glu	Pro	Asp	
					455					460					465	
	Arg	Pro	Asn	Gly	Val	Ile	Leu	Glu	Tyr	Glu	Val	Lys	Tyr	Tyr	Glu	
					470					475					480	
25	Lys	Asp	Gln	Asn	Glu	Arg	Ser	Tyr	Arg	Ile	Val	Arg	Thr	Ala	Ala	
					485					490					495	
	Arg	Asn	Thr	Asp	Ile	Lys	Gly	Leu	Asn	Pro	Leu	Thr	Ser	Tyr	Val	
					500					505					510	
30	Phe	His	Val	Arg	Ala	Arg	Thr	Ala	Ala	Gly	Tyr	Gly	Asp	Phe	Ser	
					515					520					525	
	Glu	Pro	Leu	Glu	Val	Thr	Thr	Asn	Thr	Val	Pro	Ser	Arg	Ile	Ile	
					530					535					540	
	Gly	Asp	Gly	Ala	Asn	Ser	Thr	Val	Leu	Leu	Val	Ser	Val	Ser	Gly	
					545					550					555	
35	Ser	Val	Val	Leu	Val	Val	Ile	Leu	Ile	Ala	Ala	Phe	Val	Ile	Ser	
					560					565					570	
	Arg	Arg	Arg	Ser	Lys	Tyr	Ser	Lys	Ala	Lys	Gln	Glu	Ala	Asp	Glu	
					575					580					585	

	Glu Lys His Leu Asn Gln Gly Val Arg Thr Tyr Val Asp Pro Phe	590	595	600
	Thr Tyr Glu Asp Pro Asn Gln Ala Val Arg Glu Phe Ala Lys Glu	605	610	615
5	Ile Asp Ala Ser Cys Ile Lys Ile Glu Lys Val Ile Gly Val Gly	620	625	630
	Glu Phe Gly Glu Val Cys Ser Gly Arg Leu Lys Val Pro Gly Lys	635	640	645
10	Arg Glu Ile Cys Val Ala Ile Lys Thr Leu Lys Ala Gly Tyr Thr	650	655	660
	Asp Lys Gln Arg Arg Asp Phe Leu Ser Glu Ala Ser Ile Met Gly	665	670	675
	Gln Phe Asp His Pro Asn Ile Ile His Leu Glu Gly Val Val Thr	680	685	690
15	Lys Cys Lys Pro Val Met Ile Ile Thr Glu Tyr Met Glu Asn Gly	695	700	705
	Ser Leu Asp Ala Phe Leu Arg Lys Asn Asp Gly Arg Phe Thr Val	710	715	720
20	Ile Gln Leu Val Gly Met Leu Arg Gly Ile Gly Ser Gly Met Lys	725	730	735
	Tyr Leu Ser Asp Met Ser Tyr Val His Arg Asp Leu Ala Ala Arg	740	745	750
	Asn Ile Leu Val Asn Ser Asn Leu Val Cys Lys Val Ser Asp Phe	755	760	765
25	Gly Met Ser Arg Val Leu Glu Asp Asp Pro Glu Ala Ala Tyr Thr	770	775	780
	Thr Arg Gly Gly Lys Ile Pro Ile Arg Trp Thr Ala Pro Glu Ala	785	790	795
30	Ile Ala Tyr Arg Lys Phe Thr Ser Ala Ser Asp Val Trp Ser Tyr	800	805	810
	Gly Ile Val Met Trp Glu Val Met Ser Tyr Gly Glu Arg Pro Tyr	815	820	825
	Trp Asp Met Ser Asn Gln Asp Val Ile Lys Ala Ile Glu Glu Gly	830	835	840
35	Tyr Arg Leu Pro Pro Pro Met Asp Cys Pro Ile Ala Leu His Gln	845	850	855
	Leu Met Leu Asp Cys Trp Gln Lys Glu Arg Ser Asp Arg Pro Lys	860	865	870

	Phe Gly Gln Ile Val Asn Met Leu Asp Lys Leu Ile Arg Asn Pro	
	875	880 885
	Asn Ser Leu Lys Arg Thr Gly Thr Glu Ser Ser Arg Pro Asn Thr	
	890	895 900
5	Ala Leu Leu Asp Pro Ser Ser Pro Glu Phe Ser Ala Val Val Ser	
	905	910 915
	Val Gly Asp Trp Leu Gln Ala Ile Lys Met Asp Arg Tyr Lys Asp	
	920	925 930
10	Asn Phe Thr Ala Ala Gly Tyr Thr Thr Leu Glu Ala Val Val His	
	935	940 945
	Val Asn Gln Glu Asp Leu Ala Arg Ile Gly Ile Thr Ala Ile Thr	
	950	955 960
	His Gln Asn Lys Ile Leu Ser Ser Val Gln Ala Met Arg Thr Gln	
	965	970 975
15	Met Gln Gln Met His Gly Arg Met Val Pro Val Ala Ser Thr Glu	
	980	985 990
	Thr Gln Asn Ser Asn Phe Thr Ser Ser Met His Phe Asn Arg Thr	
	995	1000 1005
20	Ala Leu Phe Leu Leu Arg Leu Arg Pro Leu Lys Leu Lys Lys Lys	
	1010	1015 1020
	Lys Lys Asn Asn Ile Cys Ser Val Ala Trp Cys Thr Asp Cys Asn	
	1025	1030 1035
	Cys Gly Ala Tyr Arg Asn Asp Cys Arg Ser Phe Glu Asp Leu Glu	
	1040	1045 1050
25	Gln Ile Val Ser Gln Lys Tyr Phe Ser Val His His Gln Ser Val	
	1055	1060 1065
	Lys Tyr Met Tyr Leu Lys Asn Thr Ala Ser Glu Phe Cys Cys Ile	
	1070	1075 1080
30	Cys Cys Gln Thr Leu Ser Phe Asp Ile Pro Asp Ser Leu Ser Ile	
	1085	1090 1095
	Trp Asn Tyr Asn Gly Arg Arg Ala Arg	
	1100	1104

(2) INFORMATION FOR SEQ ID NO:37:

- (i) SEQUENCE CHARACTERISTICS:
- 35 (A) LENGTH: 24 bases
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

TCGGATCCAC ACGNGACTCT TGGC 24

(2) INFORMATION FOR SEQ ID NO:38:

(i) SEQUENCE CHARACTERISTICS:

- 5 (A) LENGTH: 28 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

TCGGATCCAC TCAGNGACTC TINGCNGC 28

10 (2) INFORMATION FOR SEQ ID NO:39:

(i) SEQUENCE CHARACTERISTICS:

- 15 (A) LENGTH: 32 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:

CTCGAATTCC AGATAAGCGT ACCAGCACAG TC 32

(2) INFORMATION FOR SEQ ID NO:40:

(i) SEQUENCE CHARACTERISTICS:

- 20 (A) LENGTH: 32 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:40:

25 CTCGAATTCC AGATATCCGT ACCATAACAG TC 32

(2) INFORMATION FOR SEQ ID NO:41:

(i) SEQUENCE CHARACTERISTICS:

- 30 (A) LENGTH: 13 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:41:

Met Asp Tyr Lys Asp Asp Asp Asp Lys Lys Leu Ala Met
1 5 10 13

(2) INFORMATION FOR SEQ ID NO:42:

- 5 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 54 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

10 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:

CCGGATATCA TGGACTACAA GGACGACGAT GACAAGAAGC TTGCCATGGA 50

GCTC 54

(2) INFORMATION FOR SEQ ID NO:43:

- 15 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:43:

20 AGGCTGCTGG AGGAAAAGTC TG 22

(2) INFORMATION FOR SEQ ID NO:44:

- 25 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 32 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:44:

GGAGGGTGAC CTCCATGCTG CCCTTATCCT CG 32

(2) INFORMATION FOR SEQ ID NO:45:

- 30 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 9108 bases

(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:45:

5 TTCGAGCTCG CCCGACATTG ATTATTGACT AGTTATTAAT AGTAATCAAT 50
TACGGGGTCA TTAGTTCATA GCCCATATAT GGAGTTCCGC GTTACATAAC 100
TTACGGTAAA TGGCCCGCCT GGCTGACCGC CCAACGACCC CCGCCCATTG 150
ACGTCAATAA TGACGTATGT TCCCATAGTA ACGCCAATAG GGACTTTCCA 200
TTGACGTCAA TGGGTGGAGT ATTTACGGTA AACTGCCCCAC TTGGCAGTAC 250
10 ATCAAGTGTA TCATATGCCA AGTACGCCCC CTATTGACGT CAATGACGGT 300
AAATGGCCCG CCTGGCATTG TGCCCAAGTAC ATGACCTTAT GGGACTTTCC 350
TACTTGGCAG TACATCTACG TATTAGTCAT CGCTATTACC ATGGTGATGC 400
GGTTTTGGCA GTACATCAAT GGGCGTGGAT AGCGGTTTGA CTCACGGGGA 450
TTTCCAAGTC TCCACCCCAT TGACGTCAAT GGGAGTTTGT TTTGGCACCA 500
15 AAATCAACGG GACTTTCCAA AATGTCGTAA CAACTCCGCC CCATTGACGC 550
AAATGGGCGG TAGGCGTGTA CGGTGGGAGG TCTATATAAG CAGAGCTCGT 600
TTAGTGAACC GTCAGATCGC CTGGAGACGC CATCCACGCT GTTTTGACCT 650
CCATAGAAGA CACCGGGACC GATCCAGCCT CCGCGGCCCG GAACGGTGCA 700
TTGGAACGCG GATTCCCCGT GCCAAGAGTG ACGTAAGTAC CGCCTATAGA 750
20 GTCTATAGGC CCACCCCTT GGCTTCGTGA GAACGCGGCT ACAATTAATA 800
CATAACCTTA TGTATCATAC ACATACGATT TAGGTGACAC TATAGAATAA 850

CATCCACTTT GCCTTTCTCT CCACAGGTGT CCACTCCCAG GTCCAACTGC 900

ACCTCGGTTC TATCGATTGA ATTCGCGGCC GCTCGGGTCG GACCCACGCG 950

CAGCGGCCCG AGATGCAGCG GGGCGCCCGC CTGTGCCTGC GACTGTGGCT 1000

CTGCCTGGGA CTCCTGGACG GCCTGGTGAG TGGCTACTCC ATGACCCCCC 1050

5 CGACCTTGAA CATCACGGAG GAGTCACACG TCATCGACAC CGGTGACAGC 1100

CTGTCCATCT CCTGCAGGGG ACAGCACCCC CTCGAGTGGG CTTGGCCAGG 1150

AGCTCAGGAG GCGCCAGCCA CCGGAGACAA GGACAGCGAG GACACGGGGG 1200

TGGTGCGAGA CTGCGAGGGC ACAGACGCCA GGCCCTACTG CAAGGTGTTG 1250

CTGCTGCACG AGGTACATGC CAACGACACA GGCAGCTACG TCTGCTACTA 1300

10 CAAGTACATC AAGGCACGCA TCGAGGGCAC CACGGCCGCC AGCTCCTACG 1350

TGTTCTGTGAG AGACTTTGAG CAGCCATTCA TCAACAAGCC TGACACGCTC 1400

TTGGTCAACA GGAAGGACGC CATGTGGGTG CCCTGTCTGG TGTCCATCCC 1450

CGGCCTCAAT GTCACGCTGC GCTCGCAAAG CTCGGTGCTG TGGCCAGACG 1500

GGCAGGAGGT GGTGTGGGAT GACCGGCGGG GCATGCTCGT GTCCACGCCA 1550

15 CTGCTGCACG ATGCCCTGTA CCTGCAGTGC GAGACCACCT GGGGAGACCA 1600

GGACTTCCTT TCCAACCCCT TCCTGGTGCA CATCACAGGC AACGAGCTCT 1650

ATGACATCCA GCTGTTGCCC AGGAAGTCGC TGGAGCTGCT GGTAGGGGAG 1700

AAGCTGGTCC TGAAGTGCAC CGTGTGGGCT GAGTTTAACT CAGGTGTCAC 1750

CTTTGACTGG GACTACCCAG GGAAGCAGGC AGAGCGGGGT AAGTGGGTGC 1800

CCGAGCGACG CTCCCAGCAG ACCCACACAG AACTCTCCAG CATCCTGACC 1850

ATCCACAACG TCAGCCAGCA CGACCTGGGC TCGTATGTGT GCAAGGCCAA 1900

CAACGGCATC CAGCGATTTC GGGAGAGCAC CGAGGTCATT GTGCATGAAA 1950

ATCCCTTCAT CAGCGTCGAG TGGCTCAAAG GACCCATCCT GGAGGCCACG 2000

5 GCAGGAGACG AGCTGGTGAA GCTGCCCGTG AAGCTGGCAG CGTACCCCCC 2050

GGCCGAGTTC CAGTGGTACA AGGATGGAAA GGCACGTGTCC GGGCGCCACA 2100

GTCCACATGC CCTGGTGCTC AAGGAGGTGA CAGAGGCCAG CACAGGCACC 2150

TACACCCTCG CCCTGTGGAA CTCCGCTGCT GGCCTGAGGC GCAACATCAG 2200

CCTGGAGCTG GTGGTGAATG TGCCCCCCCA GATACATGAG AAGGAGGCCT 2250

10 CCTCCCCCAG CATCTACTCG CGTCACAGCC GCCAGGCCCT CACCTGCACG 2300

GCCTACGGGG TGCCCTGCC TCTCAGCATC CAGTGGCACT GGC GGCCCTG 2350

GACACCCTGC AAGATGTTTG CCCAGCGTAG TCTCCGGCGG CGGCAGCAGC 2400

AAGACCTCAT GCCACAGTGC CGTGACTGGA GGGCGGTGAC CACGCAGGAT 2450

GCCGTGAACC CCATCGAGAG CCTGGACACC TGGACCGAGT TTGTGGAGGG 2500

15 AAAGAATAAG ACTGTGAGCA AGCTGGTGAT CCAGAATGCC AACGTGTCTG 2550

CCATGTACAA GTGTGTGGTC TCCAACAAGG TGGGCCAGGA TGAGCGGCTC 2600

ATCTACTTCT ATGTGACCAC CATCCCCGAC GGCTTCACCA TCGAATCCAA 2650

GCCATCCGAG GAGCTACTAG AGGGCCAGCC GGTGCTCCTG AGCTGCCAAG 2700

CCGACAGCTA CAAGTACGAG CATCTGCGCT GGTACCGCCT CAACCTGTCC 2750

ACGCTGCACG ATGCGCACGG GAACCCGCTT CTGCTCGACT GCAAGAACGT 2800

GCATCTGTTC GCCACCCCTC TGGCCGCCAG CCTGGAGGAG GTGGCACCTG 2850

GGGCGCGCCA CGCCACGCTC AGCCTGAGTA TCCCCCGCGT CGCGCCCGAG 2900

CACGAGGGCC ACTATGTGTG CGAAGTGCAA GACCGGCGCA GCCATGACAA 2950

5 GCACTGCCAC AAGAAGTACC TGTCGGTGCA GGCCCTGGAA GCCCCTCGGC 3000

TCACGCAGAA CTTGACCGAC CTCCTGGTGA ACGTGAGCGA CTCGCTGGAG 3050

ATGCAGTGCT TGGTGGCCGG AGCGCACGCG CCCAGCATCG TGTGGTACAA 3100

AGACGAGAGG CTGCTGGAGG AAAAGTCTGG AGTCGACTTG GCGGACTCCA 3150

ACCAGAAGCT GAGCATCCAG CGCGTGCGCG AGGAGGATGC GGGACGCTAT 3200

10 CTGTGCAGCG TGTGCAACGC CAAGGGCTGC GTCAACTCCT CCGCCAGCGT 3250

GGCCGTGGAA GGCTCCGAGG ATAAGGGCAG CATGGAGATC GTGATCCTTG 3300

TCGGTACCGG CGTCATCGCT GTCTTCTTCT GGGTCCCTCCT CTCCTCATC 3350

TTCTGTAACA TGAGGAGGCC GGCCACGCA GACATCAAGA CGGGCTACCT 3400

GTCCATCATC ATGGACCCCG GGGAGGTGCC TCTGGAGGAG CAATGCGAAT 3450

15 ACCTGTCCTA CGATGCCAGC CAGTGGGAAT TCCCCGAGA GCGGCTGCAC 3500

CTGGGGAGAG TGCTCGGCTA CGGCGCCTTC GGGAAGGTGG TGGAAGCCTC 3550

CGCTTTCGGC ATCCACAAGG GCAGCAGCTG TGACACCGTG GCCGTGAAAA 3600

TGCTGAAAGA GGGCGCCACG GCCAGCGAGC ACCGCGCGCT GATGTCGGAG 3650

CTCAAGATCC TCATTCACAT CGGCAACCAC CTCAACGTGG TCAACCTCCT 3700

CGGGGCGTGC ACCAAGCCGC AGGGCCCCCT CATGGTGATC GTGGAGTTCT 3750

GCAAGTACGG CAACCTCTCC AACTTCCTGC GCGCCAAGCG GGACGCCTTC 3800

AGCCCCTGCG CGGAGAAGTC TCCCGAGCAG CGCGGACGCT TCCGCGCCAT 3850

GGTGAGCTC GCCAGGCTGG ATCGGAGGCG GCCGGGAGC AGCGACAGGG 3900

5 TCCTCTTCGC GCGGTTCTCG AAGACCGAGG GCGGAGCGAG GCGGGCTTCT 3950

CCAGACCAAG AAGCTGAGGA CCTGTGGCTG AGCCCGCTGA CCATGGAAGA 4000

TCTTGCTGCTG TACAGCTTCC AGGTGGCCAG AGGGATGGAG TTCCTGGCTT 4050

CCCGAAAGTG CATCCACAGA GACCTGGCTG CTCGGAACAT TCTGCTGTCG 4100

GAAAGCGACG TGGTGAAGAT CTGTGACTTT GGCCTTGCCC GGGACATCTA 4150

10 CAAAGACCCT GACTACGTCC GCAAGGGCAG TGCCCGGCTG CCCCTGAAGT 4200

GGATGGCCCC TGAAAGCATC TTCGACAAGG TGTACACCAC GCAGAGTGAC 4250

GTGTGGTCTT TTGGGGTGCT TCTCTGGGAG ATCTTCTCTC TGGGGGCCTC 4300

CCCGTACCCT GGGGTGCAGA TCAATGAGGA GTTCTGCCAG CGGCTGAGAG 4350

ACGGCACAAG GATGAGGGCC CCGGAGCTGG CCACTCCCGC CATACGCCGC 4400

15 ATCATGCTGA ACTGCTGGTC CGGAGACCCC AAGGCGAGAC CTGCATTCTC 4450

GGAGCTGGTG GAGATCCTGG GGGACCTGCT CCAGGGCAGG GGCCTGCAAG 4500

AGGAAGAGGA GGTCTGCATG GCCCCGCGCA GCTCTCAGAG CTCAGAAGAG 4550

GGCAGCTTCT CGCAGGTGTC CACCATGGCC CTACACATCG CCCAGGCTGA 4600

CGCTGAGGAC AGCCCGCCAA GCCTGCAGCG CCACAGCCTG GCCGCCAGGT 4650

ATTACAACCTG GGTGTCCTTT CCCGGGTGCC TGGCCAGAGG GGCTGAGACC 4700

CGTGTTTCCT CCAGGATGAA GACATTGAG GAATCCCCA TGACCCCAAC 4750

GACCTACAAA GGCTCTGTGG ACAACCAGAC AGACAGTGGG ATGGTGCTGG 4800

CCTCGGAGGA GTTTGAGCAG ATAGAGAGCA GGCATAGACA AGAAAGCGGC 4850

5 TTCAGGTAGC TGAAGCAGAG AGAGAGAAGG CAGCATACGT CAGCATTTTC 4900

TTCTCTGCAC TTATAAGAAA GATCAAAGAC TTTAAGACTT TCGCTATTTTC 4950

TTCTGCTATC TACTACAAAC TTCAAAGAGG AACCAGGAGG CCAAGAGGAG 5000

CATGAAAGTG GACAAGGAGT GTGACCACTG AAGCACCACA GGGAGGGGTT 5050

AGGCCTCCGG ATGACTGCGG GCAGGCCTGG ATAATATCCA GCCTCCCACA 5100

10 AGAAGCTGGT GGAGCAGAGT GTTCCCTGAC TCCTCCAAGG AAAGGGAGAC 5150

GCCCTTTTCAT GGTCTGCTGA GTAACAGGTG CCTTCCCAGA CACTGGCGTT 5200

ACTGCTTGAC CAAAGAGCCC TCAAGCGGCC CTTATGCCAG CGTGACAGAG 5250

GGCTCACCTC TTGCCTTCTA GGTCACCTTCT CACAATGTCC CTTCAGCACC 5300

TGACCCTGTG CCCGCCAGTT ATTCCTTGGT AATATGAGTA ATACATCAAA 5350

15 GAGTAGTGCG GCCGCGAATT CCCCGGGGAT CCTCTAGAGT CGACCTGCAG 5400

AAGCTTGGCC GCCATGGCCC AACTTGTTTA TTGCAGCTTA TAATGGTTAC 5450

AAATAAAGCA ATAGCATCAC AAATTTTACA AATAAAGCAT TTTTTTCACT 5500

GCATTCTAGT TGTGGTTTGT CCAAACATCAT CAATGTATCT TATCATGTCT 5550

GGATCGGGAA TTAATTCGGC GCAGCACCAT GGCCTGAAAT AACCTCTGAA 5600

AGAGGAACTT GGTTAGGTAC CTTCTGAGGC GGAAAGAACC AGCTGTGGAA 5650

TGTGTGTCAG TTAGGGTGTG GAAAGTCCCC AGGCTCCCCA GCAGGCAGAA 5700

GTATGCAAAG CATGCATCTC AATTAGTCAG CAACCAGGTG TGGAAAGTCC 5750

CCAGGCTCCC CAGCAGGCAG AAGTATGCAA AGCATGCATC TCAATTAGTC 5800

5 AGCAACCATA GTCCCGCCCC TAACTCCGCC CATCCCGCCC CTA ACTCCGC 5850

CCAGTTCCGC CCATTCTCCG CCCCATGGCT GACTAATTTT TTTTATTTAT 5900

GCAGAGGCCG AGGCCGCCTC GGCCTCTGAG CTATTCCAGA AGTAGTGAGG 5950

AGGCTTTTTT GGAGGCCTAG GCTTTTGCAA AAAGCTGTTA ACAGCTTGGC 6000

ACTGGCCGTC GTTTTACAAC GTCGTGACTG GGAAAACCCT GGC GTTACCC 6050

10 AACTTAATCG CCTGCAGCA CATCCCCCTT TCGCCAGCTG GCGTAATAGC 6100

GAAGAGGCCC GCACCGATCG CCCTTCCCAA CAGTTGCGCA GCCTGAATGG 6150

CGAATGGCGC CTGATGCGGT ATTTTCTCCT TACGCATCTG TCGGTATTT 6200

CACACCGCAT ACGTCAAAGC AACCATAGTA CGCGCCCTGT AGCGGCGCAT 6250

TAAGCGCGGC GGGTGTGGTG GTTACGCGCA GCGTGACCGC TACACTTGCC 6300

15 AGCGCCCTAG CGCCCGCTCC TTTCGCTTTC TTCCCTTCCT TTCTCGCCAC 6350

GTTCGCCGGC TTTCCCGTC AAGCTCTAAA TCGGGGGCTC CCTTTAGGGT 6400

TCCGATTTAG TGCTTTACGG CACCTCGACC CCAAAAACT TGATTTGGGT 6450

GATGGTTCAC GTAGTGGGCC ATCGCCCTGA TAGACGTTT TTCGCCCTTT 6500

GACGTTGGAG TCCACGTTCT TTAATAGTGG ACTCTTGTTT CAACTGGAA 6550

CAACACTCAA CCCTATCTCG GGCTATTCTT TTGATTATA AGGGATTTTG 6600

CCGATTTTCGG CCTATTGGTT AAAAAATGAG CTGATTTAAC AAAAAATTAA 6650

CGCGAATTTT AACAAAATAT TAACGTTTAC AATTTTATGG TGCACTCTCA 6700

GTACAATCTG CTCTGATGCC GCATAGTTAA GCCAGCCCCG ACACCCGCCA 6750

5 ACACCCGCTG ACGCGCCCTG ACGGGCTTGT CTGCTCCCGG CATCCGCTTA 6800

CAGACAAGCT GTGACCGTCT CCGGGAGCTG CATGTGTCAG AGGTTTTCAC 6850

CGTCATCACC GAAACGCGCG AGACGAAAGG GCCTCGTGAT ACGCCTATTT 6900

TTATAGGTTA ATGTCATGAT AATAATGGTT TCTTAGACGT CAGGTGGCAC 6950

TTTTCGGGGA AATGTGCGCG GAACCCCTAT TTGTTTATTT TTCTAAATAC 7000

10 ATTCAATAT GTATCCGCTC ATGAGACAAT AACCTGATA AATGCTTCAA 7050

TAATATTGAA AAAGGAAGAG TATGAGTATT CAACATTTC GTGTCGCCCT 7100

TATTCCTTT TTTGCGGCAT TTTGCCTTCC TGTTTTTGCT CACCCAGAAA 7150

CGCTGGTGAA AGTAAAAGAT GCTGAAGATC AGTTGGGTGC ACGAGTGGGT 7200

TACATCGAAC TGGATCTCAA CAGCGGTAAG ATCCTTGAGA GTTTTCGCCC 7250

15 CGAAGAACGT TTTCCAATGA TGAGCACTTT TAAAGTTCTG CTATGTGGCG 7300

CGGTATTATC CCGTATTGAC GCCGGGCAAG AGCAACTCGG TCGCCGCATA 7350

CACTATTCTC AGAATGACTT GGTGAGTAC TCACCACTCA CAGAAAAGCA 7400

TCTTACGGAT GGCATGACAG TAAGAGAATT ATGCAGTGCT GCCATAACCA 7450

TGAGTGATAA CACTGCGGCC AACTTACTTC TGACAACGAT CGGAGGACCG 7500

AAGGAGCTAA CCGCTTTTTT GCACAACATG GGGGATCATG TAACTCGCCT 7550

TGATCGTTGG GAACCGGAGC TGAATGAAGC CATACCAAAC GACGAGCGTG 7600

ACACCACGAT GCCTGTAGCA ATGGCAACAA CGTTGCGCAA ACTATTAACT 7650

GCGGAECTAC TTACTCTAGC TTCCCGGCAA CAATTAATAG ACTGGATGGA 7700

5 GCGGATAAA GTTGCAGGAC CACTTCTGCG CTCGGCCCTT CCGGCTGGCT 7750

GGTTTATTGC TGATAAATCT GGAGCCGGTG AGCGTGGGTC TCGCGGTATC 7800

ATTGCAGCAC TGGGGCCAGA TGGTAAGCCC TCCCGTATCG TAGTTATCTA 7850

CACGACGGGG AGTCAGGCAA CTATGGATGA ACGAAATAGA CAGATCGCTG 7900

AGATAGGTGC CTCACTGATT AAGCATTGGT AACTGTCAGA CCAAGTTTAC 7950

10 TCATATATAC TTTAGATTGA TTTAAACTT CATTTTAAAT TTAAAGGAT 8000

CTAGGTGAAG ATCCTTTTGG ATAATCTCAT GACCAAAATC CCTTAACGTG 8050

AGTTTTCGTT CCACTGAGCG TCAGACCCCG TAGAAAAGAT CAAAGGATCT 8100

TCTTGAGATC CTTTTTTTCT GCGCGTAATC TGCTGCTTGC AAACAAAAAA 8150

ACCACCGCTA CCAGCGGTGG TTTGTTTGCC GGATCAAGAG CTACCAACTC 8200

15 TTTTCCGAA GGTAAGTGGC TTCAGCAGAG CGCAGATACC AAATACTGTT 8250

CTTCTAGTGT AGCCGTAGTT AGGCCACCAC TTCAAGAACT CTGTAGCACC 8300

GCCTACATAC CTCGCTCTGC TAATCCTGTT ACCAGTGGCT GCTGCCAGTG 8350

GCGATAAGTC GTGTCTTACC GGGTTGGACT CAAGACGATA GTTACCGGAT 8400

AAGGCGCAGC GGTCGGGCTG AACGGGGGGT TCGTGACAC AGCCCAGCTT 8450

GGAGCGAACG ACCTACACCG AACTGAGATA CCTACAGCGT GAGCTATGAG 8500

AAAGCGCCAC GCTTCCCGAA GGGAGAAAGG CGGACAGGTA TCCGGTAAGC 8550

GGCAGGGTCG GAACAGGAGA GCGCACGAGG GAGCTTCCAG GGGGAAACGC 8600

CTGGTATCTT TATAGTCCTG TCGGGTTTCG CCACCTCTGA CTTGAGCGTC 8650

5 GATTTTGTG ATGCTCGTCA GGGGGGCGGA GCCTATGGAA AAACGCCAGC 8700

AACGCGGCCT TTTACGGT CCTGGCCTTT TGCTGGCCTT TTGCTCACAT 8750

GTTCTTTCCT GCGTTATCCC CTGATTCTGT GGATAACCGT ATTACCGCCT 8800

TTGAGTGAGC TGATACCGCT CGCCGAGCC GAACGACCGA GCGCAGCGAG 8850

TCACTGAGCG AGGAAGCGGA AGAGCGCCCA ATACGCAAAC CGCCTCTCCC 8900

10 CGCGCGTTGG CCGATTCATT AATGCAGCTG GCACGACAGG TTTCCCGACT 8950

GGAAAGCGGG CAGTGAGCGC AACGCAATTA ATGTGAGTTA GCTCACTCAT 9000

TAGGCACCCC AGGCTTTACA CTTTATGCTT CCGGCTCGTA TGTGTGTGG 9050

AATTGTGAGC GGATAACAAT TTCACACAGG AAACAGCTAT GACATGATTA 9100

CGAATTAA 9108

The invention claimed is:

1. An agonist antibody which activates the kinase domain of a receptor protein tyrosine kinase (pTK) selected from the group consisting of:
 - 5 a) SAL-S1;
 - b) HpTK 5; and
 - c) bpTK 7.
2. The antibody of claim 1 comprising a monoclonal antibody.
3. The antibody of claim 1 wherein the pTK is HpTK5.
- 10 4. The antibody of claim 3 having the biological characteristics of the antibody produced by the hybridoma cell line deposited under American Type Culture Collection Accession No. ATCC HB 11,583.
5. The antibody of claim 1 wherein the pTK is SAL-S1.
6. A pharmaceutical composition comprising the antibody of claim 1 in
15 an amount effective in activating the kinase domain of the receptor protein tyrosine kinase (pTK), and a pharmaceutically acceptable carrier.
7. A method for activating the kinase domain of a receptor protein tyrosine kinase (pTK) selected from the group consisting of:
 - 20 a) SAL-S1;
 - b) HpTK 5; and
 - c) bpTK 7, comprising contacting the pTK with an effective amount of an agonist antibody thereto.
8. A chimeric protein comprising a fusion of the extracellular domain
25 of a receptor protein tyrosine kinase (pTK) selected from the group consisting of:
 - a) SAL-S1;
 - b) HpTK 5; and
 - c) bpTK 7, with an immunoglobulin constant domain sequence.
- 30 9. The chimeric protein of claim 8 wherein the pTK is HpTK5.
10. The chimeric protein of claim 8 wherein the pTK is Sal-S1.
11. The chimeric protein of claim 8 wherein the immunoglobulin constant domain sequence is that of an IgG immunoglobulin.
12. A nucleic acid encoding the chimeric protein of claim 8.

13. A replicable vector comprising the nucleic acid of claim 12.
 14. A recombinant host cell comprising the nucleic acid of claim 12.
 15. A method of using a nucleic acid molecule encoding a chimeric protein comprising a fusion of the extracellular domain of a receptor
- 5 protein tyrosine kinase (pTK) selected from the group consisting of:
- a) SAL-S1;
 - b) HpTK 5; and
 - c) bpTK 7, with an immunoglobulin constant domain sequence, to
- effect the production of the chimeric protein comprising culturing the
- 10 host cell of claim 14.

FIG. 1A

GGATCCTGTG CATCAGTGAC TTAGGGCTAG GAACATTCTG CTGTCCGAAA GCGACGTGGT 60
 GAAGATCTGT GACTTTGGCC TTGCCCGGGA CATCTACAAA GACCCACAGCT ACGTCCGCAA 120
 GCATGCCCCG CTGCCCCCTGA AGTGGATGGC GCCAGAATTC 160

FIG. 1B

Asp Pro Val His Gln Xaa Leu Arg Ala Arg Asn Ile Leu Leu Ser Glu 15
 1 5 10
 Ser Asp Val Val Lys Ile Cys Asp Phe Gly Leu Ala Arg Asp Ile Tyr 30
 20 25
 Lys Asp Pro Ser Tyr Val Arg Lys His Ala Arg Leu Pro Leu Lys Trp 45
 35 40
 Met Ala Pro Glu Phe 50

FIG. 2A

GGATCCATTG	ACAGAGACCT	AGCAGCAGCG	AACATCCTGG	TCTCAGAGGA	CCTGGTAACC	60
AAGGTCAGCG	ACTTTGGCCT	GGCCAAAGCC	GAGCGGAAGG	GGCTAGACTC	AAGCCGGCTG	120
CCCGTCAANT	GGATGGCTCC	CGAATTC				147

FIG. 2B

Gly	Ser	Ile	His	Arg	Asp	Leu	Ala	Ala	Arg	Asn	Ile	Leu	Val	Ser	Glu	1	5	10	15
Asp	Leu	Val	Thr	Lys	Val	Ser	Asp	Phe	Gly	Leu	Ala	Lys	Ala	Glu	Arg	20	25	30	
Lys	Gly	Leu	Asp	Ser	Ser	Arg	Leu	Pro	Val	Lys	Trp	Met	Ala	Pro	Glu	35	40	45	
Phe																			

FIG. 3A

GTT GGA ATT CCT TCC GGC GCC ATC CAT TTC ACC GGC AGC TTT ATT TCG	48
Val Gly Ile Pro Ser Gly Ala Ile His Phe Thr Gly Ser Phe Ile Ser	15
1	
TGT CTA GAT TCA TAG ATG TCT TCA TTA TCT ACC TTA AAA ACT CTG GCA	96
Cys Leu Asp Ser Met Ser Ser Leu Ser Thr Leu Lys Thr Leu Ala	30
20	
AGT CCA AAA TCT GCT ACT TTG TAG ATA TTA TGT TCA CCA ACG AGG ACA	144
Ser Pro Lys Ser Ala Thr Leu Ile Leu Cys Ser Pro Thr Arg Thr	45
35	
TTCCT	149
Phe	

FIG. 3B

GTG CAC AGG AGT CTC GCG GCT CGG AAC ATC CTC GTC GGG GAA AAC ACC	48
Val His Arg Asp Leu Ala Ala Arg Asn Ile Leu Val Gly Glu Asn Thr	15
1	
CTC TCG AAA GTT GGG GAC TTC GGG TTA GCC AGG CTT ATC AAG GAG GAC	96
Leu Ser Lys Val Gly Asp Phe Gly Leu Ala Arg Leu Ile Lys Glu Asp	30
20	
GTC TAC CTC TCC CAT GAC CAC AAT ATC CCC TAC AAA TGG ATG GCC CCT	144
Val Tyr Leu Ser His Asp His Asn Ile Pro Tyr Lys Trp Met Ala Pro	45
35	
GAG GGA A	151
Glu Gly	
50	

FIG. 3C

GTT CAC CGA GAT CTC AAG TCC AAC AAC ATT TTG CTG CTG CAG CCC ATT 48
 Val His Arg Asp Leu Lys Ser Asn Asn Ile Leu Leu Leu Gln Pro Ile 15
 1 5 10
 GAG AGT GAC GAC ATG GAG CAC AAC ACC CTG AAG ATC ACC GAC TTT GGC 96
 Glu Ser Asp Asp Met Glu His Lys Thr Lys Ile Thr Asp Phe Gly 30
 20 25
 CTG GCC CGA GAG TGG CAC AAA ACC ACA CAA ATG AGT GCC GC 137
 Leu Ala Arg Glu Trp His Lys Thr Thr Gln Met Ser Ala 45
 35 40

FIG. 3D

GTC AAT CGT GAC CTC GCC GCC CGA AAT GTG TTG CTA GTT ACC CAA CAT 48
 Val Asn Arg Asp Leu Ala Ala Arg Asn Val Leu Leu Val Thr Gln His 15
 1 5 10
 TAC GCC AAG ATC AGT GAT TTC GGA CTT TCC AAA GCA CTG CGT GCT GAT 96
 Tyr Ala Lys Ile Ser Asp Phe Gly Leu Ser Lys Ala Leu Arg Ala Asp 30
 20 25
 GAA AAC TAC TAC AAG GCC CAG ACC CAT GGA AAG TGG CCT GTC AAG TGG 144
 Glu Asn Tyr Tyr Lys Ala Gln Thr His Gly Lys Trp Pro Val Lys Trp 45
 35 40
 TAC GCT CCG GAA TGC ATC AAC TAC TAC AAG TTC TCC AGC AAA AGC GAT 192
 Tyr Ala Pro Glu Cys Ile Asn Tyr Tyr Lys Phe Ser Ser Lys Ser Asp 60
 50 55
 GTC TGG TCC TTT GGA ATT C 211
 Val Trp Ser Phe Gly Ile 70
 65

FIG. 4A

TTCGAGCTCG CCGGACATTG ATTATTGACT AGTTATTAAAT AGTAATCAAT TACGGGGTCA 60
TTAGTTTCATA GCCCATATAT GGAGTTCCGC GTTACATAAC TTACGGTAAA TGGCCCCGCCT 120
GGCTGACCGC CCAACGACCC CCGCCCCATTG ACGTCAATAA TGACGTATGT TCCCATAGTA 180
ACGCCAATAG GGACTTTCCA TTGACGTCAA TGGGTGGAGT ATTACGGTA AACTGCCCCAC 240
TTGGCAGTAC ATCAAGTGTA TCATATGCCA AGTACGCCCC CTATTGACGT CAATGACGGT 300
AAATGGCCCG CCTGGCATTG TGCCCCAGTAC ATGACCTTAT GGGACTTTCC TACTTGGCAG 360
TACATCTACG TATTAGTCAT CGCTATTACC ATGGTGATGC GGTTTTGGCA GTACATCAAT 420
GGCGTGGAT AGCGGTTTGA CTCACGGGGA TTTCCAAGTC TCCACCCCAT TGACGTCAAT 480
GGGAGTTTGT TTTGGCACCA AAATCAACGG GACTTTCCAA AATGTCGTAA CAACTCCGCC 540
CCATTGACGC AAATGGGCGG TAGGCGTGTA CGGTGGGAGG TCTATATAAG CAGAGCTCGT 600
TTAGTGAACC GTCAGATCGC CTGGAGACGC CATCCACGCT GTTTTGACCT CCATAGAAGA 660
CACCGGGACC GATCCAGCCT CCGCGGCCGG GAACGGTGCA TTGGAACGCG GATTCCCCGT 720
GCCAAGAGTG ACGTAAGTAC CGCCTATAGA GTCTATAGGC CCACITGGCT TCGTTAGAAC 780
GCGGCTACAA TTAATACATA ACCTTATGTA TCATACACAT ACGATTTAGG TGACACTATA 840
GAATAACATC CACTTTGCCT TTCTCTCCAC AGGTGTCCAC TCCCAGGTCC AACTGCACCT 900
CGGTTCTATC GATTGAATTC CCGGGGGATC CTCTAGAGAT CCCTCGACCT CGAGATCCAT 960
TGTGCTGGCG CGGATTCTTT ATCACTGATA AGTTGGTGGA CATATTATGT TTATCAGTGA 1020

FIG. 4B

TAAAGTGTC A AGCATGACAA AGTTGCAGCC GAATACAGTG ATCCGTGCCG CCCTAGACCT 1080
GTTGAACGAG GTCGGCGTAG ACGGTCTGAC GACACGCCAA CTGGCGGAAC GGTGGGGGT 1140
TCAGCAGCCG GCGCTTTACT GGCACCTTCAG GAACAAGCGG GCGCTGCTCG ACGCACTGGC 1200
CGAAGCCATG CTGGCGGAGA ATCATAGCAC TTCCGGTGCCG AGAGCCGACG ACGACTGGCG 1260
CTCATTTCTG ACTGGGAATG CCCGCAGCTT CAGGCAGGCG CTGCTCGCCT ACCGCCAGCA 1320
CAATGGATCT CGAGGGATCT TCCATACCTA CCAGTTCTGC GCCTGCAGGT CGCGGCCGCA 1380
CTACTCTTTG ATGTATTACT CATATTACCA AGGAATAACT GCGGGGCACA GGGTCAGGTG 1440
CTGAAGGGAC ATTGTGAGAA GTGACCTAGA AGCAAGAGG TGAGCCCTCT GTCACGCTGG 1500
CATAAGGGCC GCTTGAGGGC TCTTTGGTCA AGCAGTAACG CCAGTGTCTG GGAAGGCACC 1560
TGTTACTCAG CAGACCATGA AAGGGCGTCT CCTTTCCCTT GGAGCAGTCA GCGAACACTC 1620
TGCTCCACCA GCTTCTTGTG GGAGCCTGGA TATTATCCAG GCGTGCCCGC AGTCATCCGG 1680
AGGCCTAACC CCTCCCTGTG GTGCTTCAGT GGTCACTC CTTGTCCACT TTCATGCTCC 1740
TCTTGGCCTC CTGGTTCCTC TTGGAAGTTT GTAGTAGATA GCAGAAGAAA TAGCGAAAGT 1800
CTTAAAGTCT TTGATCTTTC TTATAAGTGC AGAGAAGAAA TGCTGACGTA TGCTGCCCTTC 1860
TCTCTCTCTG CTTCAGCTAC CTGAAGCCGC TTTCTTGTCT ATACCTGCTC TCTATCTGCT 1920
CACACTCCTC CGAGGCCAGC ACCATCCCAC TGTCTGTCTG GTTGTCCACA GAGCCCTTTGT 1980
AGGTCGTTGG GGTCACTGGG AATTCCTCAA ATGTCTTCAT CCTGGAGGAA CCACGGGTCT 2040

FIG. 4C

CAGCCCCCTCT GGCAGGCAC CCGGGAAGG ACACCCAGTT GTAATACCTG GCGGCCAGGC 2100
TGTGGCGCTG CAGGCTTGSC GGGCTGTCTT CAGCGTCAGC CTGGGCGATG TGTAGGGCCA 2160
TGGTGGACAC CTGCGAGAAG CTGCCCTCTT CTGAGCTCTG AGAGCTGCGC GGGGCCATGC 2220
AGACCTCCTC TTCTCTTTGC AGGCCCCCTG CCTGGAGCAG GTCCCCCAGG ATCTCCACCA 2280
GCTCCGAGAA TGCAGGTCTC GCCTTGGGGT CTCCGGACCA GCAGTTCAGC ATGATGCGGC 2340
GTATGGCGG AGTGGCCAGC TCCGGGGCCC TCATCCTTGT GCCGTCTCTC AGCCGCTGGC 2400
AGAACTCCTC ATTGATCTGC ACCCCAGGGT ACGGGGAGGC CCCAGAGAG AGATCTCCC 2460
AGAGAAAGCAC CCCAAAGGAC CACACGTAC TCTGCGTGGT GTACACCCTG TCGAAGATGC 2520
TTTCAGGGGC CATCCACTTC AGGGGCAGCC GGGCACTGCC CTTGCGGAGC TAGTCGGGGT 2580
CTTTGTAGAT GTCCCGGGCA AGGCCAAAGT CACAGATCTT CACCACGTCG CTTTCCGACA 2640
GCAGAAATGTT CCGAGCAGCC AGGTCTCTGT GGATGCACCTT TCGGGAGGCC AGGAACTCCA 2700
TCCCTCTGGC CACCTGGAAG CTGTAGCAGA CAAGATCTTC CATGGTCAGC GGGCTCAGCC 2760
ACAGGTCCTC AGCTTCTTGG TCTGGAGAAG CCCGCCCTCGC TCCGCCCTCG GTCTTCGAGA 2820
ACCGCGCGAA GAGGACCCCTG TCGCTGCTCC CCGGCCGCCT CCGATCCAGC CTGGCGAGCT 2880
CCACCATGGC GCGGAAGCGT CCGCGCTGCT CCGGAGACTT CTCTGCGGA TGCACGAAGC 2940
TGGCTCGAGG GCGCCCAGTC GTCCGCCGCA GAGGGCCCTC CATTCGCCCG CCGCCCGCGG 3000
CGCCCCGCGAG GCCGCCCGCT CACCGNGCAG GGGCTGCGGC CGGACTCTA GAGTCGACCT 3060

FIG. 4D

GCAGAAAGCTT GGCCGCCCATG GCCCAACTTG TTTATTGCAG CTTATAATGG TTACAAATAA 3120
AGCAATAGCA TCACAAATTT CACAAATAAA GCATTTTTTT CACTGCATT C TAGTTGTGGT 3180
TTGTCCAAAC TCATCAATGT ATCTTATCAT GTCTGGATCG ATCGGGAATT AATTGGGGCG 3240
AGCACCATGG CCTGAAATAA CCTCTGAAAG AGGAACTTGG TTAGGTACCT TCTGAGGCGG 3300
AAAGAACCCAG CTGTGGAATG TGTGTCAGTT AGGGTGTGGA AAGTCCCCAG GCTCCCCAGC 3360
AGGCAGAAGT ATGCAAAAGCA TGCATCTCAA TTAGTCAGCA ACCAGGTGTG GAAAGTCCCC 3420
AGGCTCCCCA GCAGGCAGAA GTATGCAAAG CATGCATCTC AATTAGTCAG CAACCATAGT 3480
CCCGCCCCCTA ACTCCGCCCA TCCCGCCCCCT AACTCCGCC AGTTCCGCC ATTTCCGCC 3540
CCATGGCTGA CTAATTTTTT TTATTATGC AGAGGCCGAG GCCGCCCTCGG CCTCTGAGCT 3600
ATTCCAGAAG TAGTGAGGAG GCTTTTTTGG AGGCCTAGGC TTTTGCAAAA AGCTGTTAAC 3660
AGCTTGGCAC TGGCCGTCGT TTTACAACGT CGTGACTGGG AAAACCCCTGG CGTTACCCAA 3720
CTTAATCGCC TTGCAGCACA TCCCCCCTTC GCCAGCTGGC GTAATAGCGA AGAGGCCCGC 3780
ACCGATCGCC CTTCCCAACA GTTGCGTAGC CTGAATGGCG AATGGCGCCT GATGCGGTAT 3840
TTTCTCCCTA CGCATCTGTG CGGTATTTC A CACCGCATAC GTCAAAGCAA CCATAGTAGG 3900
CGCCCTGTAG CGCGGCATTA AGCGGGCGG GTGTGGTGGT TACGGCGAGC GTGACCGCTA 3960
CACTTGCCAG CGCCCTAGCG CCCGCTCCTT TCGCTTTCTT CCCTTCCTTT CTGCCCAGT 4020
TCGCCGGCTT TCCCCGTCAA GCTCTAAATC GGGGGCTCCC TTAGGGTTC CGATTAGTG 4080

FIG. 4E

CTTTACGGCA CCTCGACCCC AAAAAACTTG ATTTGGGTGA TGGTTCACGT AGTGGGCCAT 4140
 CGCCCTGATA GACGGTTTTT CGCCCTTTGA CGTTGGAGTC CACGTTCTTT AATAGTGGAC 4200
 TCTTGTTCOA AACTGGAACA ACACTCAACC CTATCTCGGG CTATTCITTT GATTATTAAG 4260
 GGATTTTGCC GATTTCGGCC TATTGGTTAA AAAATGAGCT GATTTAACAA AAATTTAACG 4320
 CGAATTTTAA CAAAATATTA ACGTTTACAA TTTTATGGTG CACTCTCAGT ACAATCTGCT 4380
 CTGATGCCGC ATAGTTAAGC CAACTCCGCT ATCGGTACGT GACTGGGTCA TGGCTGCGCC 4440
 CCGACACCCG CCAACACCCG CTGACGGGCT CTGACGGGCT TGTCTGCTCC CGGCATCCGC 4500
 TTACAGACAA GCTGTGACCG TCTCCGGGAG CTGCATGTGT CAGAGGTTTT CACCGTCATC 4560
 ACCGAAACGC GCGAGGCAGT ATTCTTGAAG ACGAAAGGSC CTCGTGATAC GCCTATTTTT 4620
 ATAGGTTAAT GTCATGATAA TAATGGTTTC TTAGACGTCA GGTGGCACTT TTCGGGGAAA 4680
 TGTGCGCGGA ACCCCTATTT GTTTATTTTT CTAAATACAT TCAAATATGT ATCCGCTCAT 4740
 GAGACAATAA CCCTGATAA TCTTCAATA ATATTGAATA AGGAAGAGTA TGAGTATTCAA 4800
 ACATTTCCGT GTCGCCCTTA TTCCCTTTTT GGCGGCATTT TGCCTTCCTG TTTTGTCTCA 4860
 CCCAGAAACG CTGGTGAAAG TAAAGATGC TGAAGATCAG TTGGGTGCAC GAGTGGGTTA 4920
 CATCGAACTG GATCTCAACA GCGGTAAGAT CCTTGAGAGT TTTCCGCCCG AAGAACGTTT 4980
 TCCAATGATG AGCACTTTTA AAGTTCTGCT ATGTGGCGCG GTATTATCCC GTGATGACGC 5040
 CCGGCAAGAG CAACTCGGTC GCCGCATACA CTATTCTCAG AATGACTTGG TTGAGTACTC 5100

FIG. 4F

ACCAGTCACA GAAAAGCATC TTACGGATGG CATGACAGTA AGAGAAATTAT GCAGTGCTGC 5160
CATAACCATG AGTGATAACA CTGCGGCCAA CTTACTTCTG ACAACGATCG GAGGACCGAA 5220
GGAGCTAACC GCTTTTGTGC ACAACATGGG GGATCATGTA ACTGCCCTTG ATCGTTGGGA 5280
ACCGGAGCTG AATGAAGCCA TACCAAAACGA CGAGCGTGAC ACCACGATGC CAGCAGCAAT 5340
GGCAACAACG TTGCGCAAAC TATTAACCTGG CGAACTACTT ACTCTAGCTT CCGGGCAACA 5400
ATTAATAGAC TGGATGGAGG CGGATAAAGT TGCAGGACCA CTTCTGGCT CGGCCCTTCC 5460
GGCTGGCTGG TTTATTGCTG ATAAATCTGG AGCCGGTGAG CGTGGGTCTC GCGGTATCAT 5520
TGCAGCACTG GGGCCAGATG GTAAGCCCTC CCGTATCGTA GTTATCTACA CGACGGGGAG 5580
TCAGGCAACT ATGGATGAAC GAAATAGACA GATCGCTGAG ATAGGTGCCT CACTGATTAA 5640
GCATTGGTAA CTGTCAGACC AAGTTTACTC ATATATACTT TAGATTGATT TAAAACTTCA 5700
TTTTTAATTT AAAAGGATCT AGGTGAAGAT CCTTTTGTAT AATCTCATGA CCAAAATCCC 5760
TTAACGTGAG TTTTCGTTCC ACTGAGCGTC AGACCCCGTA GAAAAGATCA AAGGATCTTC 5820
TTGAGATCCT TTTTCTCTGC GCGTAATCTG CTGCTTGCAA ACAAAAAAC CACCGCTACC 5880
AGCGGTGGTT TGTTCGCCG ATCAAGAGCT ACCAACTCTT TTTCCGAAGG TAACTGGCTT 5940
CAGCAGAGCG CAGATACCAA ATACTGTCTT TCTAGTGTAG CCGTAGTTAG GCCACCACTT 6000
CAAGAACTCT GTAGCACCGC CTACATACCT CGCTCTGCTA ATCCTGTTAC CAGTGGCTGC 6060
TGCCAGTGGC GATAAGTCGT GTCTTACCGG GTTGGACTCA AGACGATAGT TACCGGATAA 6120

FIG. 4G

GGCGCAGCGG TCGGGCTGAA CCGGGGGTTC GTGCACACAG CCCAGCTTGG AGCGAACGAC 6180
CTACACCGAA CTGAGATACC TACAGCGTGA GCATTGAGAA AGCGCCACGC TTCCCGAAGG 6240
GAGAAAGGCG GACAGGTATC CGGTAAGCGG CAGGGTCGGA ACAGGAGAGC GCACGAGGGA 6300
GCTTCCAGGG GGAACGCCT GGTATCTTTA TAGTCCTGTC GGGTTTCGCC ACCTCTGACT 6360
TGAGCGTCGA TTTTGTGTAT GCTCGTCAGG GGGCGGAGC CTATGGAAAA AGCCAGCAA 6420
CGCGGCCCTT TTACGGTTCC TGGCCTTTTG CTGGCCCTTTT GCTCACATGT TCTTTCCTGC 6480
GTTATCCCCCT GATTCTGTGG ATAACCGTAT TACCGCCCTTT GAGTGAGCTG ATACCGCTCG 6540
CCGCAGCCGA ACGACCGAGC GCAGCGAGTC AGTGAGCGAG GAAGCGGAAG AGCGCCCAAT 6600
ACGCAAACCG CCTCTCCCCG CGCGTTGGCC GATTCAATTAA TCCAGCTGGC ACGACAGGTT 6660
TCCCGACTGG AAAGCGGGCA GTGAGCGCAA CGCAATTAAAT GTGAGTTACC TCACTCATTA 6720
GGCACCCCG GCTTTACACT TTATGCTTCC GGCTCGTATG TTGTGTGGAA TTGTGAGCGG 6780
ATAACAATTT CACACAGGAA ACAGCTATGA CCATGATTAC GAATTAA 6827

FIG. 4H

Glu Lys Ser Pro Glu Gln Arg Gly Arg Phe Arg Ala Met Val Glu Leu 15
 1 5 10
 Ala Arg Leu Asp Arg Arg Pro Gly Ser Ser Asp Arg Val Leu Phe 30
 20 25 30
 Ala Arg Phe Ser Lys Thr Glu Gly Gly Ala Arg Arg Ala Ser Pro Asp 45
 35 40 45
 Gln Glu Ala Glu Asp Leu Trp Leu Ser Pro Leu Thr Met Glu Asp Leu 60
 50 55 60
 Val Cys Tyr Ser Phe Gln Val Ala Arg Gly Met Glu Phe Leu Ala Ser 80
 65 70 75
 Arg Lys Cys Ile His Arg Asp Leu Ala Ala Arg Asn Ile Leu Leu Ser 95
 85 90 95
 Glu Ser Asp Val Val Lys Ile Cys Asp Phe Gly Leu Ala Arg Asp Ile 110
 100 105 110
 Tyr Lys Asp Pro Asp Tyr Val Arg Lys Gly Ser Ala Arg Leu Pro Leu 125
 115 120 125
 Lys Trp Met Ala Pro Glu Ser Ile Phe Asp Lys Val Tyr Thr Thr Gln 140
 130 135 140
 Ser Asp Val Trp Ser Phe Gly Val Leu Leu Trp Glu Ile Phe Ser Leu 160
 145 150 155
 Gly Ala Ser Pro Tyr Pro Gly Val Gln Ile Asn Glu Glu Phe Cys Gln 175
 165 170 175
 Arg Leu Arg Asp Gly Thr Arg Met Arg Ala Pro Glu Leu Ala Thr Pro 190
 180 185 190

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FIG. 4I

Ala	Ile	Arg	Arg	Ile	Met	Leu	Asn	Cys	Trp	Ser	Gly	Asp	Pro	Lys	Ala
		195					200					205			
Arg	Pro	Ala	Phe	Ser	Glu	Leu	Val	Glu	Ile	Leu	Gly	Asp	Leu	Leu	Gln
		210				215					220				
Gly	Arg	Gly	Leu	Gln	Glu	Glu	Glu	Glu	Val	Cys	Met	Ala	Pro	Arg	Ser
		225			230					235					240
Ser	Gln	Ser	Ser	Glu	Glu	Gly	Ser	Phe	Ser	Gln	Val	Ser	Thr	Met	Ala
				245					250					255	
Leu	His	Ile	Ala	Gln	Ala	Asp	Ala	Glu	Asp	Ser	Pro	Pro	Ser	Leu	Gln
			260				265						270		
Arg	His	Ser	Leu	Ala	Ala	Arg	Tyr	Tyr	Asn	Trp	Val	Ser	Phe	Pro	Gly
			275				280					285			
Cys	Leu	Ala	Arg	Gly	Ala	Glu	Thr	Arg	Gly	Ser	Ser	Arg	Met	Lys	Thr
		290				295					300				
Phe	Glu	Glu	Phe	Pro	Met	Thr	Pro	Thr	Thr	Tyr	Lys	Gly	Ser	Val	Asp
		305			310					315					320
Asn	Gln	Thr	Asp	Ser	Gly	Met	Val	Leu	Ala	Ser	Glu	Glu	Cys	Glu	Gln
				325			330							335	
Ile	Glu	Ser	Arg	Tyr	Arg	Gln	Glu	Ser	Gly	Phe	Arg	*			
			340				345								

FIG. 5A

```

FTCGAGCTCG CCGGACATTG ATTATTGACT AGTTATTAAAT AGTAATCAAT TACGGGCTCA    60
TTAGTTTCATA GCCCATATAT GGAGTTCCGC GTTACATAAC TTACGGTAAA TGGCCCCGCCT    120
GGCTGACCGC CCAACGACCC CCGCCCATTG ACGTCAATAA TGACGTATGT TCCCATAGTA    180
ACGCCAATAG GGACTTTTCCA TTGACGTCAA TGGGTGGAGT ATTTACGGTA AACTGCCCCAC    240
TTGGCAGTAC ATCAAGTGTA TCATATGCCA AGTACGCCCC CTATTGACGT CAATGACGGT    300
AAATGGCCCC CCTGGCATTG TGCCCCAGTAC ATGACCTTAT GGGACITTTCC TACTTGGCAG    360
TACATCTACG TATTAGTCAT CGCTATTACC ATGGTGATGC GGTFTTTGGCA GTACATCAAT    420
GGCGTGGAT AGCGGTTTGA CTCACGGGGA TTTCCAAGTC TCCACCCCCAT TGACGTCAAT    480
GGGAGTTTGT TTTGGCACCA AAATCAACGG GACTTTCCAA AATGTCGTAA CAACTCCGCC    540
CCATTGACGC AAATGGGCGG TAGGCGTGTA CGGTGGGAGG TCTATATAAG CAGAGCTCGT    600
TTAGTGAACC GTCAGATCGC CTGGAGACGC CATCCACGCT GTTTTGACCT CCATAGAAGA    660
CACCGGGACC GATCCAGCCT CCGCGGGCGG GAACGGTGCA TTGGAACGGG GATTCCCCCGT    720
GCCAAGAGTG ACGTAAAGTAC CGCCTATAGA GTCTATAGGC CCACCTTGGCT TCGTTAGAAC    780
GCGGCTACAA TTAATACATA ACCTTATGTA TCATACACAT ACGATTTAGG TGACACTATA    840
GAATAACATC CACTTTGCCT TTCTCTCCAC AGGTGTCCAC TCCCAGGTCC AACTGCACCT    900
CGGTTCTATC GATTGAATTC CCCGGGGGATC CTCTAGAGAT CCCTCGACCT CGAGTCGACT    960
TTTTTTTTTT TTTTGTAGG CCAAGGGTA CTTCTTTTC TTTATTAATT ACTCAGAAGT    1020

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FIG. 5B

CTAGGCCACA GCAATCTACT GTTCTCCTCT CATTTTCCTA AACTATTTTG ATACCTATTT 1080
CTCAGACTTT ATGGGCTATT AGACATTTCT CACATTTCCA TAGATAATAA CTCATCCGTT 1140
TTGCAACCTG ATTCTCAATA TTAAGAGATT AAAACTAATG TATATGACTC TCAGTTGACA 1200
CATACTGAAG TACAGAAAAA TTCCATCATT TCCTTCTGCA AAATGAAAAA GACTTCGTTT 1260
TCTCAACAGC TGCATCATTT TTTTATGCAT AGAAAAAAT GTGCAATTAC TCCAAGTACA 1320
ATCAAGTCAT TTAACATGGC TTTACCATCA TTGTAGTTAC AGGATATTTT AAAAGAGAAA 1380
AAAAATCTC AAAGCACAGG TCCTGCTGTG CAGCAAAGCA ATCAAATTCC TTCATAATAA 1440
CAGCCTGATG GGATTCAGCA ATCTGAGGAA TAATGAATAA CCACTCTAAT CAGTAAACAG 1500
GAAAATGCTA CAACAGTCAC TGAGTAAAAA TTGGACTATC ATCTGTTGAT TCTCTTGATC 1560
GACATTTCAA ACAATAAATG GAAATGTAAG TATCTCTTAA AAAGAAAAAT AACTTGGTTT 1620
AGTGTGCTTA ATTTTACCAG GCAGTGAGGA AATTATATAT CACCTTGACT GTCCTGCAGT 1680
GTTGCCCAGT CAATAAAAATG CACAAAATAAT CTTTTTCATA ATACATGGCC AACTTTATCC 1740
TATCACCTGA ATATGTCAGG ATAAACTGAT TGTGCAGTTG GTTGATAACA TTGTATTTTG 1800
GAATGGATTA TTTGAATTTG TTTTGCTACT TTATTATTTG ATATTCTTCT CCAGTGTTC A 1860
TCTTATGAAG TTATTTGTCAT CTGAATATGA AGAGTCTGTT TCAAAAATAGT CTTCAAGTTT 1920
CCAACGCAGT GTCTCAAATG TAGGTCGTTT CTTAGGCTCT GCATTCCAGC ACTCCAACAT 1980
GATGTTGTAA AATTGCTGTG GACAGTTGGA TGGTTGCGGA AGTCTATAGT TTTGAGCCAA 2040

FIG. 5C

CATCTGGATT ACCTGGGCAC CTGTCAATACC ACTGTAAGGC ATTTTGCCAT AAGTAATGAT 2100
TTCATAAAGA AGGATTCCAA ATGACCATAC ATCGGACTTA ATGCTGAATT TATTACTACG 2160
AATGGCTTCG GCGCAGTCC ACTTCACCGG CAGCTTTAAT TCGTGTCTAG ATTCATAGAT 2220
GTC TTCATTA TCTACCTTAA AAACCTCTGGC AAGTCCAAA TCTGCTACTT TGTAGATATT 2280
ATGTTACCA ACGAGGACAT TTCTGGCAGC CAGATCTCTG TGAATGTAGT TCCGAGACTC 2340
CAGATAGGCC ATTCCAGAGG CAACCTGTGC CGCCATGTCT ACCTGTGTGAG TCAGATGGAT 2400
TTTTGATCCA GTGTCAATTT GGAGATATTC TTGCAGACTT CCATGTCTCA TCAACTCTGT 2460
AATAATATAA ATTGGATCTT CTAAAGTGCA AACAGCATAA AGCTGGATAA GCTTTGGATG 2520
TCTTAGGTTT TTCATTATCT GTGCCTCCCT CAGGAAGTCA TTTGGATCCA TTGAACCTGG 2580
TTTTAATGTT TTCACGTGCTA CTGGAGTGGT ATTGTTCCAC AGACCTTCCC ATACTTCGCC 2640
AACTGACCA GATCCCAATC GCTTCAGAAG CTGTATGGAG TTGCGGTCTA TCTCCCATG 2700
GTCCACGGTT TTATACGACA AATCAAATGG AGCTGGGACC TGGATCTTTA AGCATGGTTT 2760
CCCCAGCTTG ACACACAGGC CGTCACTTGT CTTGGGTGAG TGGCTCACA AATCGTTTCAG 2820
TGTTGAAAAG ATTCTTCTTC GCGTGAGAAA AAATCCCCCT TCATCCAGTC TTTTAATCT 2880
GTAGTGTTTT ACAACTGCTC CATCTAAAC TGAAAGAGAG AATTCTCCTT TTTGGCTTTC 2940
ACTTCTCTG ATTAGAAAG AACCGGTCTT GTTTTCTGAA TATAATAGTT GTTCTCTG 3000
ATCTGATCTT CCGATTGCTC CAAAGAACCA CGGCTCTGCC TGTAGGCTTC TGTCTCTCAGC 3060

FIG. 5D

CACGTAGTGA GAAGGAATAT AGCCTTGTAG TTGCTGACTG GAGCCATCTC GTCTTTTCTC 3120
CAAGTGTCTG GCAAACCCACC AGCCCTCATG CAAAGTGTCC AGAACTTGAA GTTTGTCAAC 3180
TGCTCGGAAG CTCGAAGTCCT CAGCAGTCCG AGCCTGGTAA TCAAAACAAAG CCACAAAGTA 3240
GTGGCCCATGC CTCGTGTGACT GGGGAGAGCA AAGGGCCCTT GATTTTCAA TCACGGTTGA 3300
CTTGTCTGCC TCCGTGGACA AACAGGGGAG ATAGGGTTCT AGGTACTCCC AGAGCCTCTG 3360
ACAGATGTTG CTCATTGTGC CTTGGTGGGG AGAAGAGGAG CAGGGCTTCT CCCTCTCCCC 3420
TTAGTCTCTG CGATCCACCT TATCTTCCTT CACCAGGCAA CTTTGAAGTC AGCACCAACT 3480
CACCATACTT CGGAGAGTAT GCAAAGTCCC GTTTCAGATC AGTCCAGCAG CTGGGTTGCA 3540
GCAAAGTCCTA CCTGGAGAGA CTTACCGGCT TGCTTCTCTG GGTGGAGGT GCTACCCCGA 3600
GGCAAAACTG AGCAGGAGCT GGGCAGCTGC TCACTAGGAA GGTGTCTTTT CTTCCTTATCT 3660
GCTTAAGAAT CCCACAACAA AATAAAATA AATTAAAG GGCTTTATTT AGACAAATAT 3720
CTGAGAACAG AATGGTGCCA TCTTGCCCTT TGTCCCAATA AAAAGTTAGC AAGAGGAAGC 3780
TACTAAACCC TGGTAAACCC TCCACGTCTT GCTTTCGCCA GGTTCGACTC GAGGGATCTT 3840
CCATACCTAC CAGTTCTGCG CCTGCAGGTC GCGGCCGCGA CTCTAGAGTC GACCTGCAGA 3900
AGCTTGGCCG CCATGGCCCA ACTTGTTTAT TGCAGCTTAT AATGGTTACA AATAAAGCAA 3960
TAGCATCACA AATTTCACAA ATAAAGCATT TTTTTCACCTG CATCTAGTT GTGGTTGTC 4020
CAAACTCATC AATGTATCTT ATCATGTCTG GATCGGGAAT TAATTCCGGC CAGCACCATG 4080

FIG. 5E

GCCTGAAATA ACCTCTGAAA GAGGAACTTG GTTAGGTACC TTCTGAGGCG GAAAGAACCA 4140
 GCTGTGGAAT GTGTGTCAGT TAGGGTGTGG AAAGTCCCCA GGCTCCCCAG CAGGCAGAAG 4200
 TATGCAAAGC ATGCATCTCA ATTAGTCAGC AACCAGGTGT GGAAAGTCCC CAGGCTCCCC 4260
 AGCAGGCAGA AGTATGCAAA GCATGCATCT CAATTAGTCA GCAACCATAG TCCCCGCCCT 4320
 AACTCCGCCC ATCCCGCCCC TAACTCCGCC CAGTTCGGCC CATTCTCCGC CCCATGGCTG 4380
 ACTAATTTTT TTTATTTATG CAGAGGCCGA GGCCGGCCTCG GCCTCTGAGC TATTCCAGAA 4440
 GTAGTGAGGA GGCTTTTTTG GAGGCCTAGG CTTTGTGCAA AAGCTGTTAA CAGCTTGGCA 4500
 CTGGCCGTCG TTTTACAACG TCGTGA CTGG GAAAACCCCTG GCGTTACCCA ACTTAATCGC 4560
 CTTGCAGCAC ATCCCCCTTT CGCCAGCTGG CGTAATAGCG AAGAGGCCCG CACCGATCGC 4620
 CCTTCCCAAC AGTTGCGCAG CCTGAATGGC GAATGGCGCC TGATGCGGTA TTTTCTCCTT 4680
 ACGCATCTGT GCGGTATTTC ACACCGCATA CGTCAAAAGCA ACCATAGTAC GCGCCCTGTA 4740
 GCGGGCGATT AAGCGCGGCG GGTGTGGTGG TTACGGCGCAG CGTGACCGCT ACACTTGCCA 4800
 GCGCCCTAGC GCGCGCTCCT TTCGCTTTCT TCCCTTCCTT TCTCGCCACG TTCGCCGGCT 4860
 TTCCCCGTCA AGCTCTAAAT CGGGGGCTCC CTTTAGGGTT CCGATTAGT GCTTTACGGC 4920
 ACCTCGACCC CAAAAACTT GATTTGGGTG ATGTTTCACG TAGTGGGCCA TCGCCCTGAT 4980
 AGACGGTTTT TCGCCCTTTG ACGTTGGAGT CCACGTTCTT TAATAGTGA CTCTTGTTC 5040
 AAACTGGAAC AACACTCAAC CCTATCTCGG GCTATTCTTT TGATTATATA GGGATTTTGC 5100

FIG. 5F

CGATTTCGGC CTATTGGTTA AAAAATGAGC TGAATTAAACA AAAATTAAAC GCGAATTTTA 5160
ACAAAATATT AACGTTTACA ATTTTATGGT GCACTCTCAG TACAATCTGC TCTGATGCCG 5220
CATAGTTAAG CCAGCCCCGA CACCCGCCAA CACCCGCTGA CGCGCCCTGA CGGGCTTGTC 5280
TGCTCCCGC ATCCGCTTAC AGACAAGCTG TGACCGTCTC CGGGAGCTGC ATGTGTCAGA 5340
GGTTTTCACC GTCATCACCG AAACGGCGGA GACGAAAGGG CCTCGTGATA CGCCTATTTT 5400
TATAGGTTAA TGTCA TGTCATGATA ATAATGGTTT CTTAGACGTC AGGTGGCACT TTTCGGGGAA 5460
ATGTGCGCGG AACCCCTATT TGTTTATTTT TCTAAATACA TTCAAATATG TATCCGCTCA 5520
TGAGACAATA ACCCTGATAA ATGCTTCAAT AATATTGAAA AAGGAAGAGT ATGAGTATTC 5580
AACATTTCCG TGTCGGCCCTT ATTCCCTTTT TTGCGGCATT TTGCCCTTCTT GTTTTIGCTC 5640
ACCCAGAAAC GCTGGTGAAA GTAAAAGATG CTGAAGATCA GTTGGGTGCA CGAGTGGGTT 5700
ACATCGAACT GGATCTCAAC AGCGGTAAGA TCCTTGAGAG TTTTCGCCCC GAAGAACGTT 5760
TTCCAATGAT GAGCACTTTT AAAGTTCTGC TATGTGGCGC GGTATTATCC CGTATTGACG 5820
CCGGGCAAGA GCAACTCGGT CGCCGCATAC ACTATTCTCA GAATGACTTG GTTGAGTACT 5880
CACCAGTCAC AGAAAAGCAT CTTACGGATG GCATGACAGT AAGAGAATTA TGCAGTGCTG 5940
CCATAACCAT GAGTGATAAC ACTGCGGCCA ACTTACTTCT GACAACGATC GGAGGACCGA 6000
AGGAGCTAAC CGCTTTTTTG CACAACATGG GGGATCATGT AACTCGCCTT GATCGTTGGG 6060
AACCGGAGCT GAATGAAGCC ATACCAAACG ACGAGCGTGA CACCACGATG CCTGTAGCAA 6120

FIG. 5G

TGGCAACAAC GTTGGGCAAA CTATTAACTG GCGAACTACT TACTCTAGCT TCCCGGCAAC 6180
AATTAATAGA CTGGATGGAG GCGGATAAAG TTGCAGGACC ACTTCTGCGC TCGGCCCTTC 6240
CGGCTGGCTG GTTTATTGCT GATAAATCTG GAGCCGGTGA GCGTGGGTCT CGCGGTATCA 6300
TTGCAGCACT GGGGCCAGAT GGTAAGCCCT CCCGTATCGT AGTTATCTAC ACGACGGGGA 6360
GTCAGGCAAC TATGGATGAA CGAAATAGAC AGATCGCTGA GATAGGTGCC TCACTGATTA 6420
AGCATTGGTA ACTGTCAGAC CAAGTTTACT CATATATACT TTAGATTGAT TTAAAACTTC 6480
ATTTTAAATT TAAAAGGATC TAGGTGAAGA TCCTTTTGA TAATCTCATG ACCAAATCC 6540
CTTAAACGTA GTTTTCGTTT CACTGAGCGT CAGACCCCGT AGAAAAGATC AAAGGATCTT 6600
CTTGAGATCC TTTTTFCTG CGCGTAATCT GCTGCTTGCA AACAAAAA CCACCGCTAC 6660
CAGCGGTGGT TTGTTTGCCG GATCAAGAGC TACCAACTCT TTTTCCGAAG GTAACCTGGT 6720
TCAGCAGAGC GCAGATACCA AATACTGTTT TTCTAGTGA GCGGTAGTTA GGCCACCACT 6780
TCAAGAACTC TGTAGCACCG CCTACATACC TCGCTCTGCT AATCCTGTGA CCAGTGGCTG 6840
CTGCCAGTGG CGATAAGTCG TGTCTTACC GGTGGGACTC AAGACGATAG TTACCGGATA 6900
AGGCGCAGCG GTCGGGCTGA ACGGGGGTT CGTGACACA GCCCAGCTTG GAGCGAACGA 6960
CCTACACCGA ACTGAGATAC CTACAGCGTG AGCTATGAGA AAGCGCCACG CTTCCCGAAG 7020
GGAGAAAGGC GGACAGGTAT CCGGTAAGCG GCAGGGTCGG AACAGGAGAG CGCAGGAGGG 7080
AGCTTCCAGG GGGAAACGCC TGGTATCTTT ATAGTCTCTG CCGGTTTCGC CACCTCTGAC 7140

FIG. 5H

TTGAGCGTCG	ATTTTGTGA	TGCTCGTCAG	GGGGGGGAG	CCTATGGAA	AACGCCAGCA	7200
ACGCGGCCTT	TTTACGGTTC	CTGGCCCTTT	GCTGGCCTTT	TGCTCACATG	TTCTTTCCCTG	7260
CGTTATCCCC	TGATTCTGTG	GATAACCGTA	TTACCGCCCTT	TGAGTGAGCT	GATACCGCTC	7320
GCCGCAGCCG	AACGACCGAG	CGCAGCGAGT	CAGTGAGCGA	GGAAGCGGA	GAGCGCCCAA	7380
TACGCAAACC	GCCTCTCCCC	GCGCGTTGGC	CGATTCATTA	ATGCAGCTGG	CACGACAGGT	7440
TTCCCGACTG	GAAAGCGGCC	AGTGAGCGCA	ACGCAATTAA	TGTGAGTTAG	CTCACTCATT	7500
AGGCACCCCA	GGCTTTACAC	TTTATGCTTC	CGGCTCGTAT	GTTGTGTGA	ATTGTGAGCG	7560
GATAACAATT	TCACACAGGA	AACAGCTATG	ACATGATTAC	GAATTAA		7607

FIG. 5I

Met Ser Asn Ile Cys Gln Arg Leu Trp Glu Tyr Leu Glu Pro Tyr Leu
 1 5 10 15
 Pro Cys Leu Ser Thr Glu Ala Asp Lys Ser Thr Val Ile Glu Asn Pro
 20 25 30
 Gly Ala Leu Cys Ser Pro Gln Ser Gln Arg His Gly His Tyr Phe Val
 35 40 45
 Ala Leu Phe Asp Tyr Gln Ala Arg Thr Ala Glu Asp Leu Ser Phe Arg
 50 55 60
 Ala Gly Asp Lys Leu Gln Val Leu Asp Thr Leu His Glu Gly Trp Trp
 65 70 75 80
 Phe Ala Arg His Leu Glu Lys Arg Arg Asp Gly Ser Ser Gln Gln Leu
 85 90 95
 Gln Gly Tyr Ile Pro Ser Asn Tyr Val Ala Glu Asp Arg Ser Leu Gln
 100 105 110
 Ala Glu Pro Trp Phe Phe Gly Ala Ile Gly Arg Ser Asp Ala Glu Lys
 115 120 125
 Gln Leu Leu Tyr Ser Glu Asn Lys Thr Gly Ser Phe Leu Ile Arg Glu
 130 135 140
 Ser Glu Ser Gln Lys Gly Glu Phe Ser Leu Ser Val Leu Asp Gly Ala
 145 150 155 160
 Val Val Lys His Tyr Arg Ile Lys Arg Leu Asp Glu Gly Gly Phe Phe
 165 170 175
 Leu Thr Arg Arg Arg Ile Phe Ser Thr Leu Asn Glu Phe Val Ser His
 180 185 190

FIG. 5J

Tyr Thr Lys Thr Ser Asp Gly Leu Cys Val Lys Leu Gly Lys Pro Cys
 195 200 205
 Leu Lys Ile Gln Val Pro Ala Pro Phe Asp Leu Ser Tyr Lys Thr Val
 210 215 220
 Asp Gln Trp Glu Ile Asp Arg Asn Ser Ile Gln Leu Leu Lys Arg Leu
 225 230 235 240
 Gly Ser Gly Gln Phe Gly Glu Val Trp Glu Gly Leu Trp Asn Asn Thr
 245 250 255
 Thr Pro Val Ala Val Lys Thr Leu Lys Pro Gly Ser Met Asp Pro Asn
 260 265 270
 Asp Phe Leu Arg Glu Ala Gln Ile Met Lys Asn Leu Arg His Pro Lys
 275 280 285
 Leu Ile Gln Leu Tyr Ala Val Cys Thr Leu Glu Asp Pro Ile Tyr Ile
 290 295 300
 Ile Thr Glu Leu Met Arg His Gly Ser Leu Gln Glu Tyr Leu Gln Asn
 305 310 315 320
 Asp Thr Gly Ser Lys Ile His Leu Thr Gln Gln Val Asp Met Ala Ala
 325 330 335
 Gln Val Ala Ser Gly Met Ala Tyr Leu Glu Ser Arg Asn Tyr Ile His
 340 345 350
 Arg Asp Leu Ala Ala Arg Asn Val Leu Val Gly Glu His Asn Ile Tyr
 355 360 365
 Lys Val Ala Asp Phe Gly Leu Ala Arg Val Phe Lys Val Asp Asn Glu
 370 375 380

FIG. 5K

Asp Ile Tyr Glu Ser Arg His Glu Ile Lys Leu Pro Val Lys Trp Thr	385	390	395	400
Ala Pro Glu Ala Ile Arg Ser Asn Lys Phe Ser Ile Lys Ser Asp Val	405	410	415	
Trp Ser Phe Gly Ile Leu Tyr Glu Ile Ile Thr Tyr Gly Lys Met	420	425	430	
Pro Tyr Ser Gly Met Thr Gly Ala Gln Val Ile Gln Met Leu Ala Gln	435	440	445	
Asn Tyr Arg Leu Pro Gln Pro Ser Asn Cys Pro Gln Gln Phe Tyr Asn	450	455	460	
Ile Met Leu Glu Cys Trp Asn Ala Glu Pro Lys Glu Arg Pro Thr Phe	465	470	475	480
Glu Thr Leu Arg Trp Lys Leu Glu Asp Tyr Phe Glu Thr Asp Ser Ser	485	490	495	
Tyr Ser Asp Ala Asn Asn Phe Ile Arg *	500	505		

FIG. 6

GCGGCCGCGAG	AGAAAGCAGA	GGATGGGGCT	TAGCAGCTGG	CAGAGCCAGG	AGCGGGGAGG	60
TAGCAGAAAG	ACCACAAGTA	CAAAGAAGTC	CTGAAACTTT	GGTTTGTGCTG	CTGCAGCCCA	120
TTGAGAGTGA	CGACATGGAG	CACAAGACCC	TGAAGATCAC	CGACTTTGGC	CTGGCCCCGAG	180
AGTGGCACAA	AACCACACAA	ATGAGTGCCG	CNGGCACCTA	CNCCTGGATG	GCTCCTGAGG	240
TTATCAAGGC	CTCCACCTTC	TCTAAGGGCA	GTGACGTCTG	GAGTTTGGG	GTGCTGCTGT	300
GGGAACTGCT	GACCGGGGAG	NTGCCATACC	GTGGCATTGA	CTGCCCTTGCT	GTGGCCTATG	360
GCGTAGCTGT	TAACAAGCTC	ACACTGCCAT	CCATCCACCT	GGCC		404

FIG. 7A

ATGAGAGCGT TGGCGGCGGA CGGCGGCCAG CTGCCGCTGC TCGTTGTTTT TTCTGCAATG 60
ATATTTGGGA CTATTACAAA TCAAGATCTG CCTGTGATCA AGTGTGTTTT AATCAATCAT 120
AAGAAACAATG ATTATCAGT GGGGAAGTCA TCATCATATC CCATGGTATC AGAATCCCCG 180
GAAGACCTCG GGTGTGCGTT GAGACCCCG AGCTCAGGA CAGTGTACGA AGCTGCCGCT 240
GTGGAAGTGG ATGTATCTGC TTCCATCACA CTGCAAGTGC TGGTCGATGC CCCAGGGAAC 300
ATTTCTGTG TCTGGGTCTT TAAGCACAGC TCCCTGAATT GCCAGCCACA TTTTGATTTA 360
CAAAACAGAG GAGTTGTTTC CATCGTCATT TTGAAAATGA CAGAAACCCA AGCTGGAGAA 420
TACCTACTTT TTATTCAGAG TGAAGCTACC AATTACACAA TATTGTTTAC AGTGAGTATA 480
AGAAATACCC TGCTTTACAC ATTAAGAAGA CCTTACTTTA GAAAAATGGA AAACCAGGAC 540
GCCCTGGTCT GCATATCTGA GAGCGTTCCA GAGCGGATCC TGGAAATGGGT GCTTTGGGAT 600
TCACAGGGGG AAAGCTGTAA AGAAGAAAGT CCAGCTGTTG TTAATAAGGA GGAATAAGTG 660
CTTCATGAAT TATTGGGAC GGACATAAAG TGCTGTGCCA GAAATGAACT GGGCAGGGAA 720
TGCACCAGGC TGTTACAAAT AGATCTAAAT CAAACTCCTC AGACCACATT GCCACAATTA 780
TTTCTTAAAG TAGGGGAACC CTTATGGATA AGGTGCAAAG CTGTTTCATGT GAACCATGGA 840
TTCCGGGCTCA CCTGGGAATT AGAAAAACAA GCACTCGAGG AGGGCAACTA CTTTGAGATG 900
AGTACCTATT CAACAAACAG AACTATGATA CGGATTCTGT TTGCTTTTGT ATCATCAGTG 960
GCAAGAAACG ACACCGGATA CTACACTTGT TCCTCTTCAA AGCATCCCAG TCAATCAGCT 1020
TTGGTTACCA TCGTAGAAAA GGGATTATA AATGCTACCA ATTCAAGTGA AGATTATGAA 1080

FIG. 7B

ATTGACCAAT ATGAAGAGTT TTGTTTTTCT GTCAGGTTTA AAGCCTACCC ACAATCAGA	1140
TGTACGTGGA CCTTCTCTCG AAAATCATTT CCTTGTGAGC AAAAGGGTCT TGATAACGGA	1200
TACAGCATAT CCAAGTTTIG CAATCATAAG CACCAGCCAG GAGAAATATAT ATTCCATGCA	1260
GAAATGATG ATGCCCAATT TACCAAAATG TTCACGCTGT ATATAAGAAG GAAACCTCAA	1320
GTCCTCGCAG AAGCTTCGGC AAGTCAGGCG TCCTGTTTCT CGGATGGATA CCCATTACCA	1380
TCTTGGACCT GGAAGAAGTG TTCAGACAAG TCTCCCAACT GCACAGAAGA GATCACAGAA	1440
GGAGTCTGGA ATAGAAAGGC TAACAGAAAA GTGTTTGGAC AGTGGGTGTC GAGCAGTACT	1500
CTAAACATGA GTGAAGCCAT AAAAGGGTTC CTGGTCAAGT GCTGTGCATA CAATTCCCTT	1560
GGCACATCTT GTGAGACGAT CCTTTTAAAC TCTCCAGGCC CCTTCCCTTT CATCCAAGAC	1620
AACATCTCAT TCTATGCAAC AATTGGTGTT TGTCTCCTCT TCATTGTGCT TTTAACCCTG	1680
CTAATTGTC ACAAGTACAA AAAGCAATTT AGGTATGAAA GCCAGCTACA GATGGTACAG	1740
GTGACCGGAT CCTCAGATTA TGAGTACTTC TACGTTGATT TCAGAGAATA TGAATATGAT	1800
GTCAAAATGGG AGTTTCCAAG AGAAAATTTA GAGTTTGGGA AGGTACTAGG ATCAGGTGCT	1860
TTTGGAAAAG TGATGAACGC AACAGCTTAT GGAATTAGCA AAACAGGAGT CTCAAATCCAG	1920
GTTACCGTCA AAATGCTGAA AGAAAAGCA GACAGCTCTG AAAGAGAGGC ACTCATGTCA	1980
GAACTCAAGA TGATGACCCA GCTGGGAAGC CACGAGAATA TTGTGAACCT GCTGGGGGCG	2040
TGCACACTGT CAGGACCAAT TTACTTGATT TTTGAATACT GTTGCTATGG TGATCTTCTC	2100
AACTATCTAA GAAGTAAAG AGAAAATTT CACAGGACTT GGACAGAGAT TTTCAAGGAA	2160

FIG. 7C

CACAATTTC A GTTTTTTACC CACTTTCCAA TCACATCCAA ATTCCAGCAT GCCTGGTTCA 2220
AGAGAAGTTC AGATACACCC GGACTCGGAT CAAATCTCAG GGC TTCATGG GAATTCATTT 2280
CACTCTGAAG ATGAAATTGA ATATGAAAC CAAAAAGGC TGGAGAAGA GGAGGACTTG 2340
AATGTGCTTA CATTTGAAGA TCTTCTTTGC TTTCATATC AAGTTGCCAA AGGAATGGAA 2400
TTTCTGGAAT TTAAGTCGTG TGTTACAGA GACCTGGCCG CCAGGAACGT GCTTGTCCAC 2460
CACGGGAAG TGGTGAAGAT ATGTGACTTT GGATTGGCTC GAGATATCAT GAGTGATTCC 2520
AACTATGTTG TCAGGGGCAA TGCCCGTCTG CCTGTAAAT GGATGGCCCC CGAAAGCCTG 2580
TTTGAAGGCA TCTACACCAT TAAGAGTGAT GTCTGGTCAT ATGGAATATT ACTGTGGGAA 2640
ATCTTCTCAC TTGGTGTGAA TCCTTACCCT GGCAATCCGG TTGATGCTAA CTTCTACAAA 2700
CTGATTCAAA ATGGATTTAA AATGGATCAG CCATTTTATG CTACAGAAGA AATATACATT 2760
ATAATGCAAT CCTGCTGGGC TTTTGACTCA AGGAAACGGC CATCCTTCCC TAATTGACT 2820
TCGTTTTTAG GATGTCAGCT GGCAGATGCA GAAGAAGCGA TGTATCAGAA TGTGGATGGC 2880
CGTGTTCGG AATGTCCTCA CACCTACCAA AACAGGCGAC CTTTCAGCAG AGAGATGGAT 2940
TTGGGGCTAC TCTCTCGCA GGCTCAGGTC GAAGATTCTG AGAGGAACAA TTTAGTTTTA 3000
AGGACTTCAT CCTCCACCT ATCCCTAACA GGCTGTAGAT TACCAAAACA AGGTTAATTT 3060
CATCACTAAA AGAAAATCTA TTATCAACTG CTGCTTCACC AGACTTTTCT CTAGAGAGCG 3120

FIG. 8A

TCGGCGTCCA	CCGCCCCCAGG	GAGAGTCAGA	CCTGGGGGGG	CGAGGGCCCC	CCAAACTCAG	60
TTCGGATCCT	ACCCGAGTGA	GGCGGCGCC	ATG GAG	CTC CGG	GTG CTG	113
	Met	Glu	Leu	Arg	Val	5
						1
TGG GCT	TCG TTG	GCC GCA	GCT TTG	GAA GAG	ACC CTG	161
Trp	Ala	Ser	Leu	Ala	Glu	15
						10
						20
						25
						30
						35
						40
						45
						50
						55
						60
						65
						70
						75
						80
						85
						90
						95
						100
						105
						110
						115
						120
						125
						130
						135

FIG. 8B

AAG GTG GAC ACG GTG GCC GCG GAG CAT CTC ACC CGG AAG CGC CCT GGG Lys Val Asp Thr Val Ala Ala Glu His Leu Thr Arg Lys Arg Pro Gly 140 145 150	545
GCC GAG GCC ACC GGG AAG GTG AAT GTC AAG ACG CTG CGT CTG GGA CCG Ala Glu Ala Thr Gly Lys Val Asn Val Lys Thr Leu Arg Leu Gly Pro 155 160 165	593
CTC AGC AAG GCT GGC TTC TAC CTG GCC TTC CAG GAC CAG GGT GCC TGC Leu Ser Lys Ala Gly Phe Tyr Leu Ala Phe Gln Asp Gln Gly Ala Cys 170 175 180	641
ATG GCC CTG CTA TCC CTG CAC CTC TTC TAC AAA AAG TGC GCC CAG CTG Met Ala Leu Leu Ser Leu His Leu Phe Tyr Lys Lys Cys Ala Gln Leu 185 190 195 200	689
ACT GTG AAC CTG ACT CGA TTC CCG GAG ACT GTG CCT CGG GAG CTG GTT Thr Val Asn Leu Thr Arg Phe Pro Glu Thr Val Pro Arg Glu Leu Val 205 210 215	737
GTG CCC GTG GCC GGT AGC TGC GTG GTG GAT GCC GTC CCC GCC CCT GGC Val Pro Val Ala Gly Ser Cys Val Val Asp Ala Val Pro Ala Pro Gly 220 225 230	785
CCC AGC CCC AGC CTC TAC TGC CGT GAG GAT GGC CAG TGG GCC GAA CAG Pro Ser Pro Ser Leu Tyr Cys Arg Glu Asp Gly Gln Trp Ala Glu Gln 235 240 245	833
CCG GTC ACG GGC TGC AGC TGT GCT CCG GGG TTC GAG GCA GCT GAG GGG Pro Val Thr Gly Cys Ser Cys Ala Pro Gly Phe Glu Ala Ala Glu Gly 250 255 260	881
AAC ACC AAG TGC CGA GCC TGT GCC CAG GGC ACC TTC AAG CCC CTG TCA Asn Thr Lys Cys Arg Ala Cys Ala Gln Gly Thr Phe Lys Pro Leu Ser 265 270 275 280	929

FIG. 8C

GGA GAA GGG TCC TGC CAG CCA TGC CCA GCC AAT AGC CAC TCT AAC ACC Gly Glu Gly Ser Cys Gln Pro Cys Pro Ala Asn Ser His Ser Asn Thr 285 290 295	977
ATT GGA TCA GCC GTC TGC CAG TGC CGC GTC GGG TAC TTC CGG GCA CGC Ile Gly Ser Ala Val Cys Gln Cys Arg Val Gly Tyr Phe Arg Ala Arg 300 305 310	1025
ACA GAC CCC CGG GGT GCA CCC TGC ACC ACC CCT CCT TCG GCT CCG CGG Thr Asp Pro Arg Gly Ala Pro Cys Thr Thr Pro Pro Ser Ala Pro Arg 315 320 325	1073
AGC GTG GTT TCC CGC CTG AAC GGC TCC TCC CTG CAC CTG GAA TGG AGT Ser Val Val Ser Arg Leu Asn Gly Ser Ser Leu His Leu Glu Trp Ser 330 335 340	1121
GCC CCC CTG GAG TCT GGT GGC CGA GAG GAC CTC ACC TAC GCC CTC CGC Ala Pro Leu Glu Ser Gly Gly Arg Glu Asp Leu Thr Tyr Ala Leu Arg 345 350 355 360	1169
TGC CGG GAG TGC CGA CCC GGA GGC TCC TGT GCG CCC TGC GGG GGA GAC Cys Arg Glu Cys Arg Pro Gly Gly Ser Cys Ala Pro Cys Gly Gly Asp 365 370 375	1217
CTG ACT TTT GAC CCC GGC CCC CGG GAC CTG GTG GAG CCC TGG GTG GTG Leu Thr Phe Asp Pro Gly Pro Arg Asp Leu Val Glu Pro Trp Val Val 380 385 390	1265
GTT CGA GGG CTA CGT CCT GAC TTC ACC TAT ACC TTT GAG GTC ACT GCA Val Arg Gly Leu Arg Pro Asp Phe Thr Tyr Thr Phe Glu Val Thr Ala 395 400 405	1313
TTG AAC GGG GTA TCC TCC TTA GCC ACG GGC CCC GTC CCA TTT GAG CCT Leu Asn Gly Val Ser Ser Leu Ala Thr Gly Pro Val Pro Phe Glu Pro 410 415 420	1361

FIG. 8D

GTC AAT GTC ACC ACT GAC CGA GAG GTA CCT CCT GCA GTG TCT GAC ATC Val Asn Val Thr Thr Asp Arg Glu Val Pro Pro Ala Val Ser Asp Ile 425 430 440	1409
CGG GTG ACG CGG TCC TCA CCC AGC AGC TTG AGC CTG GCC TGG GCT GTT Arg Val Thr Arg Ser Ser Pro Ser Ser Leu Ser Leu Ala Trp Ala Val 445 450 455	1457
CCC CGG GCA CCC AGT GGG GCT GTG CTG GAC TAC GAG GTC AAA TAC CAT Pro Arg Ala Pro Ser Gly Ala Val Leu Asp Tyr Glu Val Lys Tyr His 460 465 470	1505
GAG AAG GGC GCC GAG GGT CCC AGC AGC GTG CGG TTC CTG AAG ACG TCA Glu Lys Gly Ala Glu Glu Gly Pro Ser Ser Val Arg Phe Leu Lys Thr Ser 475 480 485	1553
GAA AAC CGG GCA GAG CTG CGG GGG CTG AAG CGG GGA GCC AGC TAC CTG Glu Asn Arg Ala Glu Leu Arg Gly Leu Lys Arg Gly Ala Ser Tyr Leu 490 495 500	1601
GTG CAG GTA CGG GCG CGC TCT GAG GCC GGC TAC GGG CCC TTC GGC CAG Val Gln Val Arg Ala Arg Ser Glu Ala Glu Tyr Gly Pro Phe Gly Gln 505 510 515 520	1649
GAA CAT CAC ACG CAG ACC CAA CTG GAT GAG AGC GAG GGC TGG CCG GAG Glu His His Ser Gln Thr Gln Leu Asp Glu Ser Glu Gly Trp Arg Glu 525 530 535	1697
CAG CTG GCC CTG ATT GCG GGC ACG GCA GTC GTG GGT GTG GTC CTG GTC Gln Leu Ala Leu Ile Ala Glu Thr Ala Val Val Gly Val Val Leu Val 540 545 550	1745
CTG GTG GTC ATT GTG GTC GCA GTT CTC TGC CTC AGG AAG CAG AGC AAT Leu Val Val Ile Val Val Ala Val Leu Cys Leu Arg Lys Gln Ser Asn 555 560 565	1793

FIG. 8E

GGG AGA GAA GCA GAA TAT TCG GAC AAA CAC GGA CAG TAT CTC ATC GGA Gly Arg Glu Ala Glu Tyr Ser Asp Lys His Gly Gln Tyr Leu Ile Gly 570 575 580	1841
CAT GGT ACT AAG GTC TAC ATC GAC CCC TTC ACT TAT GAA GAC CCT AAT His Gly Thr Lys Val Tyr Ile Asp Pro Phe Thr Tyr Glu Asp Pro Asn 585 590 595 600	1889
GAG GCT GTG AGG GAA TTT GCA AAA GAG ATC GAT GTC TCC TAC GTC AAG Glu Ala Val Arg Glu Phe Ala Lys Glu Ile Asp Val Ser Tyr Val Lys 605 610 615	1937
ATT GAA GAG GTG ATT GGT GCA GGT GAG TTT GGC GAG GTG TGC CGG GGG Ile Glu Glu Val Ile Gly Ala Glu Gly Phe Gly Glu Val Cys Arg Gly 620 625 630	1985
CGG CTC AAG GCC CCA GGG AAG AAG GAG AGC TGT GTG GCA ATC AAG ACC Arg Leu Lys Ala Pro Gly Lys Lys Glu Ser Cys Val Ala Ile Lys Thr 635 640 645	2033
CTG AAG GGT GGC TAC ACG GAG GAG CCG CCG CGT GAG TTT CTG AGC GAG Leu Lys Gly Gly Tyr Thr Glu Arg Gln Arg Arg Glu Phe Leu Ser Glu 650 655 660	2081
GCC TCC ATC ATG GGC CAG TTC GAG CAC CCC AAT ATC ATC CGC CTG GAG Ala Ser Ile Met Gly Gln Phe Glu His Pro Asn Ile Ile Arg Leu Glu 665 670 675 680	2129
GGC GTG GTC ACC AAC AGC ATG CCC GTC ATG ATT CTC ACA GAG TTC ATG Gly Val Val Thr Asn Ser Met Pro Val Met Ile Leu Thr Glu Phe Met 685 690 695	2177
GAG AAC GGC GCC CTG GAC TCC TTC CTG CGG CTA AAC GAC GGA CAG TTC Glu Asn Gly Ala Leu Asp Ser Phe Leu Arg Leu Asn Asp Gly Gln Phe 700 705 710	2225

FIG. 8F

ACA GTC ATC CAG CTC GTG GGC ATG CTG CGG GGC ATC GCC TCG GGC ATG Thr Val Ile Gln Leu Val Gly Met Leu Arg Gly Ile Ala Ser Gly Met 715 720 725	2273
CGG TAC CTT GCC GAG ATG AGC TAC GTC CAC CGA GAC CTG GCT GCT CGC Arg Tyr Leu Ala Glu Met Ser Tyr Val His Arg Asp Leu Ala Ala Arg 730 735 740	2321
AAC ATC CTA GTC AAC AGC AAC CTC GTC TGC AAA GTG TCT GAC TTT GGC Asn Ile Leu Val Asn Ser Asn Leu Val Cys Lys Val Ser Asp Phe Gly 745 750 755 760	2369
CTT TCC CGA TTC CTG GAG AAC TCT TCC GAT CCC ACC TAC ACC AGC Leu Ser Arg Phe Leu Glu Glu Asn Ser Ser Asp Pro Thr Tyr Thr Ser 765 770 775	2417
TCC CTG GGA GGA AAG ATT CCC ATC CGA TGG ACT GCC CCG GAG GCC ATT Ser Leu Gly Gly Lys Ile Pro Ile Arg Trp Thr Ala Pro Glu Ala Ile 780 785 790	2465
GCC TTC CGG AAG TTC ACT TCC GCC AGT GAT GCC TGG AGT TAC GGG ATT Ala Phe Arg Lys Phe Thr Ser Ala Ser Asp Ala Trp Ser Tyr Gly Ile 795 800 805	2513
GTG ATG TGG GAG GTG ATG TCA TTT GGG GAG AGG CCG TAC TGG GAC ATG Val Met Trp Glu Val Met Ser Phe Gly Glu Arg Pro Tyr Trp Asp Met 810 815 820	2561
AGC AAT CAG GAC GTG ATC AAT GCC ATT GAA CAG GAC TAC CGG CTG CCC Ser Asn Gln Asp Val Ile Asn Ala Ile Glu Gln Asp Tyr Arg Leu Pro 825 830 835 840	2609
CCG CCC CCA GAC TGT CCC ACC TCC CTC CAC CAG CTC ATG CTG GAC TGT Pro Pro Pro Asp Cys Pro Thr Ser Leu His Gln Leu Met Leu Asp Cys 845 850 855	2657

FIG. 8G

TGG CAG AAA GAC CGG AAT GCC CGG CCC CGC TTC CCC CAG GTG GTC AGC Trp Gln Lys Asp Arg Asn Ala Arg Pro Arg Phe Pro Gln Val Val Ser 860 865 870	2705
GCC CTG GAC AAG ATG ATC CGG AAC CCC GCC AGC CTC AAA ATC GTG GCC Ala Leu Asp Lys Met Ile Arg Asn Pro Ala Ser Leu Lys Ile Val Ala 875 880 885	2753
CGG GAG AAT GGC GGG GCC TCA CAC CCT CTC CTG GAC CAG CGG CAG CCT Arg Glu Asn Gly Gly Ala Ser His Pro Leu Leu Asp Gln Arg Gln Pro 890 895 900	2801
CAC TAC TCA GCT TTT GGC TCT GTG GGC GAG TGG CTT CGG GCC ATC AAA His Tyr Ser Ala Phe Gly Ser Val Gly Glu Trp Leu Arg Ala Ile Lys 905 910 915 920	2849
ATG GGA AGA TAC GAA GAA AGT TTC GCA GCC GCT GGC TTT GGC TCC TTC Met Gly Arg Tyr Glu Glu Ser Phe Ala Ala Ala Gly Phe Gly Ser Phe 925 930 935	2897
GAG CTG GTC AGC CAG ATC TCT GCT GAG GAC CTG CTC CGA ATC GGA GTC Glu Leu Val Ser Gln Ile Ser Ala Glu Asp Leu Leu Arg Ile Gly Val 940 945 950	2945
ACT CTG GCG GGA CAC CAG AAG AAA ATC TTG GCC AGT GTC CAG CAC ATG Thr Leu Ala Gly His Gln Lys Lys Ile Leu Ala Ser Val Gln His Met 955 960 965	2993
AAG TCC CAG GCC AAG CCG GGA ACC CCG GGT GGG ACA GGA GGA CCG GCC Lys Ser Gln Ala Lys Pro Gly Thr Pro Gly Gly Thr Gly Gly Pro Ala 970 975 980	3041
CCG CAG TAC TGA CCT GCA GGA ACT CCC CAC CCC AGG GAC ACC GCC TCC Pro Gln Tyr * Pro Ala Gly Thr Pro His Pro Arg Asp Thr Ala Ser 985 990 995 1000	3089

FIG. 8H

CCA TTT TCC GGG GCA GAG TGG GGA CTC ACA GAG GCC CCC AGC CCT GTG Pro Phe Ser Gly Ala Glu Trp Gly Leu Thr Glu Ala Pro Ser Pro Val 1005 1010 1015	3137
CCC CGC TGG ATT GCA CTT TGA GCC CGT GGG GTG AGG AGT TGG CAA TTT Pro Arg Trp Ile Ala Leu * Ala Arg Gly Val Arg Ser Trp Gln Phe 1020 1025 1030	3185
GGA GAG ACA GGA TTT GGG GGT TCT GCC ATA ATA GGA GGG GAA AAT CAC Gly Glu Thr Gly Phe Gly Gly Ser Ala Ile Ile Gly Gly Glu Asn His 1035 1040 1045	3233
CCC CCA GCC ACC TCG GGG AAC TCC AGA CCA AGG GTG AGG GCG CCT TTC Pro Pro Ala Thr Ser Gly Asn Ser Arg Pro Arg Val Arg Ala Pro Phe 1050 1055 1060	3281
CCT CAG GAC TGG GTG TGA CCA GAG GAA AAG GAA GTG CCC AAC ATC TCC Pro Gln Asp Trp Val * Pro Glu Glu Lys Glu Val Pro Asn Ile Ser 1065 1070 1075 1080	3329
CAG CCT CCC CAG GTG CCC CCC TCA CCT TGA TGG GTG CGT TCC CGC AGA Gln Pro Pro Gln Val Pro Pro Ser Pro * Trp Val Arg Ser Arg Arg 1085 1090 1095	3377
CCA AAG AGA GTG TGA CTC CCT TGC CAG CTC CAG AGT GGG GGT GTC Pro Lys Arg Val * Leu Pro Cys Gln Leu Gln Ser Gly Gly Ala Val 1100 1105 1110	3425
CCA GGG GGC AAG AAG GGG TGT CAG GGC CCA GTG ACA AAA TCA TTG GGG Pro Gly Gly Lys Lys Gly Cys Gln Gly Pro Val Thr Lys Ser Leu Gly 1115 1120 1125	3473
TTT GTA GTC CCA ACT TGC TGC TGT CAC CAC CAA ACT CAA TCA TTT TTT Phe Val Val Pro Thr Cys Cys His His Gln Thr Gln Ser Phe Phe 1130 1135 1140	3521

FIG. 8I

TCC CTT GTA AAT GCC CCT CCC CCA GCT GCT GCC TTC ATA TTG AAG GTT 3569
 Ser Leu Val Asn Ala Pro Pro Ala Ala Phe Ile Leu Lys Val 1145
 1150
 TTT GAG TTT TGT TTT TGG TCT TAA TTT TTC TCC CCG TTC CCT TTT TGT 3617
 Phe Glu Phe Cys Phe Trp Ser * Phe Phe Ser Pro Phe Pro Phe Cys 1165
 1170
 TTC TTC GTT TTG TTT TTC TAC CGT CCT TGT CAT AAC TTT GTG TTG GAG 3665
 Phe Phe Val Leu Phe Phe Tyr Arg Pro Cys His Asn Phe Val Leu Glu 1180
 1185
 GGA ACC TGT TTC ACT ATG GCC TCC TTT GCC CAA GTT GAA ACA GGG GCC 3713
 Gly Thr Cys Phe Thr Met Ala Ser Phe Ala Gln Val Glu Thr Gly Ala 1195
 1200
 CAT CAT CAT GTC TGT TTC CAG AAC AGT GCC TTG GTC ATC CCA CAT CCC 3761
 His His His Val Cys Phe Gln Asn Ser Ala Leu Val Ile Pro His Pro 1210
 1215
 CGG ACC CCG CCT GGG ACC CCC AAG CTG TGT CCT ATG AAG GGG TGT GGG 3809
 Arg Thr Pro Pro Gly Thr Pro Lys Leu Cys Pro Met Lys Gly Cys Gly 1225
 1230
 GTG AGG TAG TGA AAA GGG CCG TAG TTG GTG GAA CCC AGA AAC GGA 3857
 Val Arg * * Lys Gly Arg * Leu Val Val Glu Pro Arg Asn Gly 1245
 1250
 CGC CGG TGC TTG GAG GGG TTC TTA AAT TAT ATT TAA AAA AGT AAC TTT 3905
 Arg Arg Cys Leu Glu Gly Phe Leu Asn Tyr Ile * Lys Ser Asn Phe 1260
 1265
 TTG TAT AAA TAA AAG AAA ATG GGA CGT GTC CCA GCT CCA GGG GTA 3950
 Leu Tyr Lys * Lys Lys Met Gly Arg Val Pro Ala Pro Gly Val 1275
 1280
 AAAAAAAAAA AAAAAAAAAA 3969

FIG. 9

Ala Arg Asn Ile Leu Val Asn Ser Asn Leu Val Cys Lys Val Ser Asp
 1 5 10 15
 Phe Gly Leu Ser Arg Phe Leu Glu Asp Thr Ser Asp Pro Thr Tyr
 20 25 30
 Thr Ser Ala Leu Gly Gly Lys Ile Pro Met Arg Trp Thr Ala Pro Glu
 35 40 45
 Ala Ile Gln Tyr Arg Lys Phe Ala Ser Ala Ser
 50 55

FIG. 10

Asn Val Leu Val Lys Ser Pro Asn His Val Lys Ile Thr Asp Phe Gly
 1 5 10 15
 Leu Ala Arg Leu Leu Glu Gly Asp Glu Lys Glu Tyr Asn Ala Asp Gly
 20 25 30
 Gly Lys Met Pro Ile Lys Trp Met Ala Leu Glu Cys Ile His Tyr Arg
 35 40 45
 Lys Phe Thr His Gln Ser
 50

FIG. 11

Asn Cys Met Leu Ala Gly Asp Met Thr Val Cys Val Ala Asp Phe Gly
 1 5 10 15
 Leu Ser Trp Lys Ile Tyr Ser Gly Ala Thr Ile Val Arg Gly Cys Ala
 20 25 30
 Ser Lys Leu Pro Val Lys Trp Leu Ala Leu Gly Ser Leu Ala Asp Asn
 35 40 45
 Leu Tyr Thr Val His Ser
 50

FIG. 12

Asn Cys Leu Val Gly Lys Asn Tyr Thr Ile Lys Ile Ala Asp Phe Gly
 1 5 10 15
 Met Ser Arg Asn Leu Tyr Ser Gly Asp Tyr Tyr
 20 25

FIG. 13

Thr Arg Asn Ile Leu Val Glu Asn Glu Asn Arg Val Lys Ile Gly Asp
 1 5 10 15
 Phe Gly Leu Thr Lys Val Leu Pro Gln Asp Lys Glu Tyr Tyr Lys Val
 20 25 30
 Lys Glu Pro Gly Glu Ser Pro Ile Phe Trp Tyr Ala Pro Glu Ser Leu
 35 40 45
 Thr Glu Ser Leu Phe Ser Val Ala Ser Asp
 50 55

FIG. 14

Ala Arg Asn Ile Leu Val Asn Ser Asn Leu Val Cys Lys Val Ser Asp
 1 5 10 15
 Phe Gly Met Ser Arg Val Leu Glu Asp Asp Pro Glu Ala Ala Tyr Thr
 20 25 30
 Thr Arg Gly Gly Lys Ile Pro Ile Arg Trp Thr Ala Pro Glu Ala Ile
 35 40 45
 Ala Tyr Arg Lys Phe Thr Ser Ala Ser Asp
 50 55

FIG. 15A

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1  TCGGGTCGGA CCCACGCGCA GCGGCCGGAG ATGCAGCGGG GCGCCGCGCT GTGCCTGCGA
   AGCCCAGCCT GGGTGCGCGT CGCCGGCCTC TACGTCGCCC CGCGGCGCGA CACGGACGCT
1  M Q R G A A L C L R

61 CTGTGGCTCT GCCTGGGACT CCTGGACGGC CTGGTGAGTG GCTACTCCAT GACCCCCCG
   GACACCGAGA CGGACCCTGA GGACCTGCCG GACCACTCAC CGATGAGGTA CTGGGGGGGC
11 L W L C L G L L D G L V S G Y S M T P P

121 ACCTTGAACA TCACGGAGGA GTCACACGTC ATCGACACCG GTGACAGCCT GTCCATCTCC
   TGGAACTTGT AGTGCCTCCT CAGTGTGCAG TAGCTGTGGC CACTGTGCGA CAGGTAGAGG
31 T L N I T E E S H V I D T G D S L S I S

181 TGCAGGGGAC AGCACCCCT CGAGTGGGCT TGGCCAGGAG CTCAGGAGGC GCCAGCCACC
   ACGTCCCCTG TCGTGGGGGA GCTCACCCGA ACCGCTCCTC GAGTCCTCCG CGGTGCGTGG
51 C R G Q H P L E W A W P G A Q E A P A T

241 GGAGACAAGG ACAGCGAGGA CACGGGGGTG GTGCGAGACT GCGAGGGCAC AGACGCCAGG
   CCTCTGTTCC TGTCGCTCCT GTGCCCCAC CACGCTCTGA CGCTCCCGTG TCTGCGGTCC
71 G D K D S E D T G V V R D C E G T D A R

301 CCCTACTGCA AGGTGTTGCT GCTGCACGAG GTACATGCCA ACGACACAGG CAGCTACGTC
   GGGATGACGT TCCACAACGA CGACGTGCTC CATGTACGGT TGCTGTGTCC GTGATGTCAG
91 P Y C K V L L L H E V H A N D T G S Y V

361 TGCTACTACA AGTACATCAA GGCACGCATC GAGGGCACCA CGGCCGCCAG CTCCTACGTG
   ACGATGATGT TGATGTAGTT CCGTGCCTAG CTCCCGTGGT GCCGGCGGTC GAGGATGCAC
111 C Y Y K Y I K A R I E G T T A A S S Y V

421 TTCGTGAGAG ACTTTGAGCA GCCATTTCATC AACAAGCCTG ACACGCTCTT GGTCACAGG
   AAGCACTCTC TGAAACTCGT CCGTAAGTAG TTGTTCCGGAC TGTGCGAGAA CCAGTTGTCC
131 F V R D F E Q P F I N K P D T L L V N R

481 AAGGACGCCA TGTGGGTGCC CTGTCTGGTG TCCATCCCCG GCCTCAATGT CACGCTGCGC
   TTCCTGCGGT ACACCCACGG GACAGACCAC AGGTAGGGGC CGGAGTTACA GTGCGACGCG
151 K D A M W V P C L V S I P G L N V T L R

541 TCGCAAAGCT CGGTGCTGTG GCCAGACGGG CAGGAGGTGG TGTGGGATGA CCGGCGGGGC
   AGCGTTTTCGA GCCACGACAC CCGTCTGCCC GTCTCCACC ACACCCTACT GGCCGCCCGC
171 S Q S S V L W P D G Q E V V W D D R R G

601 ATGCTCGTGT CCACGCCACT GCTGCACGAT GCCCTGTACC TGCAGTGCGA GACCACCTGG
   TACGAGCACA GGTGCGGTGA CGACGTGCTA CGGGACATGG ACGTCACGCT CTGGTGGACC
191 M L V S T P L L H D A L Y L Q C E T T W

661 GGAGACCAGG ACTTCCTTTC CAACCCCTTC CTGGTGACCA TCACAGGCAA CGAGCTCTAT
   CCTCTGGTCC TGAAGGAAAG GTTGGGGAAG GACCACGTGT AGTGTCCGTT GCTCGAGATA
211 G D Q D F L S N P F L V H I T G N E L Y

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FIG. 15B

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721 GACATCCAGC TGTGCCCCAG GAAGTCGCTG GAGCTGCTGG TAGGGGAGAA GCTGGTCCTG
    CTGTAGGTTCG ACAACGGGTC CTTTCAGCGAC CTCGACGACC ATCCCTCTTT CGACCAGGAC
231 D I Q L L P R K S L E L L V G E K L V L

781 AACTGCACCG TGTGGGCTGA GTTTAACTCA GGTGTCACCT TTGACTGGGA CTACCCAGGG
    TTGACGTGGC ACACCCGACT CAAATTGAGT CCACAGTGGA AACTGACCCT GATGGGTCCC
251 N C T V W A E F N S G V T F D W D Y P G

841 AAGCAGGCAG AGCGGGGTAA GTGGGTGCCC GAGCGACGCT CCCAGCAGAC CCACACAGAA
    TTCGTCCGTC TCGCCCATTT CACCCACGGG CTCGCTGCGA GGGTCGTCTG GGTGTGTCTT
271 K Q A E R G K W V P E R R S Q Q T H T E

901 CTCTCCAGCA TCCTGACCAT CCACAACGTC AGCCAGCACG ACCTGGGCTC GTATGTGTGC
    GAGAGGTTCGT AGGACTGGTA GGTGTGTGAG TCGGTCTGTC TGGACCCGAG CATACACACG
291 L S S I L T I H N V S Q H D L G S Y V C

961 AAGGCCAACA ACGGCATCCA GCGATTTTCGG GAGAGCACCG AGGTCATTGT GCATGAAAAT
    TTCCGGTTGT TGCCGTAGGT CGCTAAAGCC CTCTCGTGGC TCCAGTAACA CGTACTTTTA
311 K A N N G I Q R F R E S T E V I V H E N

1021 CCCTTCATCA GCGTCGAGTG GCTCAAAGGA CCCATCCTGG AGGCCACGGC AGGAGACGAG
    GGGAAAGTAGT CGCAGCTCAC CGAGTTTCCT GGGTAGGACC TCCGGTGCCG TCCTCTGCTC
331 P F I S V E W L K G P I L E A T A G D E

1081 CTGGTGAAGC TGCCCGTGAA GCTGGCAGCG TACCCCCCGC CCGAGTTCCA GTGGTACAAG
    GACCACTTCG ACGGGCACTT CGACCGTCGC ATGGGGGGCG GGCTCAAGGT CACCATGTTC
351 L V K L P V K L A A Y P P P E F Q W Y K

1141 GATGGAAAGG CACTGTCCGG GCGCCACAGT CCACATGCC TGGTGCTCAA GGAGGTGACA
    CTACCTTTCC GTGACAGGCC CGCGGTGTCA GGTGTACGGG ACCACGAGTT CCTCCACTGT
371 D G K A L S G R H S P H A L V L K E V T

1201 GAGGCCAGCA CAGGCACCTA CACCCTCGCC CTGTGGAAC TCGCTGCTGG CCTGAGGCGC
    CTCCGGTTCGT GTCCGTGGAT GTGGGAGCGG GACACCTTGA GGCACGACC GGACTCCGCG
391 E A S T G T Y T L A L W N S A A G L R R

1261 AACATCAGCC TGGAGCTGGT GGTGAATGTG CCCCCCAGA TACATGAGAA GGAGGCCCTC
    TTGTAGTCGG ACCTCGACCA CCACTTACAC GGGGGGGTCT ATGTACTCTT CCTCCGGAGG
411 N I S L E L V V N V P P Q I H E K E A S

1321 TCCCCAGCA TCTACTCGCG TCACAGCCGC CAGGCCCTCA CCTGCACGGC CTACGGGGTG
    AGGGGGTTCGT AGATGAGCGC AGTGTGCGCG GTCCGGGAGT GGACGTGCCG GATGCCCCAC
431 S P S I Y S R H S R Q A L T C T A Y G V

1381 CCCCTGCCTC TCAGCATCCA GTGGCACTGG CGGCCCTGGA CACCCTGCAA GATGTTTGCC
    GGGGACGGAG AGTCGTAGGT CACCGTGACC GCCGGGACCT GTGGGACGTT CTACAAACGG
451 P L P L S I Q W H W R P W T P C K M F A

1441 CAGCGTAGTC TCCGGCGGCG GCAGCAGCAA GACCTCATGC CACAGTGCCG TGACTGGAGG
    GTCGCATCAG AGGCCGCCGC CGTCGTGCTT CTGGAGTACG GTGTCACGGC ACTGACCTCC
471 Q R S L R R R Q Q Q D L M P Q C R D W R

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FIG. 15C

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1501 GCGGTGACCA CGCAGGATGC CGTGAACCCC ATCGAGAGCC TGGACACCTG GACCGAGTTT
      CGCCACTGGT GCGTCCTACG GCACTTGGGG TAGCTCTCGG ACCTGTGGAC CTGGCTCAAA
491  A V T T   Q D A   V N P   I E S L   D T W   T E F

1561 GTGGAGGGAA AGAATAAGAC TGTGAGCAAG CTGGTGATCC AGAATGCCAA CGTGTCTGCC
      CACCTCCCTT TCTTATTCTG ACACTCGTTC GACCACTAGG TCTTACGGTT GCACAGACGG
511  V E G K   N K T   V S K   L V I Q   N A N   V S A

1621 ATGTACAAGT GTGTGGTCTC CAACAAGGTG GGCCAGGATG AGCGGCTCAT CTA CTCTCTAT
      TACATGTTCA CACACCAGAG GTTGTTCAC CCGGTCCTAC TCGCCGAGTA GATGAAGATA
531  M Y K C   V V S   N K V   G Q D E   R L I   Y F Y

1681 GTGACCACCA TCCCCGACGG CTTCACCATC GAATCCAAGC CATCCGAGGA GCTACTAGAG
      CACTGGTGGT AGGGGCTGCC GAAGTGGTAG CTTAGGTTTCG GTAGGCTCCT CGATGATCTC
551  V T T I   P D G   F T I   E S K P   S E E   L L E

1741 GGCCAGCCGG TGCTCCTGAG CTGCCAAGCC GACAGCTACA AGTACGAGCA TCTGCGCTGG
      CCGGTCGGCC ACGAGGACTC GACGGTTCGG CTGTGCGATGT TCATGCTCGT AGACGCGACC
571  G Q P V   L L S   C Q A   D S Y K   Y E H   L R W

1801 TACCGCCTCA ACCTGTCCAC GCTGCACGAT GCGCACGGGA ACCCGCTTCT GCTCGACTGC
      ATGGCGGAGT TGGACAGGTG CGACGTGCTA CGCGTGCCCT TGGGCGAAGA CGAGCTGACG
591  Y R L N   L S T   L H D   A H G N   P L L   L D C

1861 AAGAACGTGC ATCTGTTTCG CACCCCTCTG GCCGCCAGCC TGGAGGAGGT GGCACCTGGG
      TTCCTGCACG TAGACAAGCG GTGGGGAGAC CGGCGGTTCG ACCTCCTCCA CCGTGGACCC
611  K N V H   L F A   T P L   A A S L   E E V   A P G

1921 GCGCGCCACG CCACGCTCAG CCTGAGTATC CCCC GCGTCG CGCCCGAGCA CGAGGGCCAC
      CGCGCGGTGC GGTGCGAGTC GGACTCATAG GGGGCGCAGC GCGGGCTCGT GCTCCCGGTG
631  A R H A   T L S   L S I   P R V A   P E H   E G H

1981 TATGTGTGCG AAGTGCAAGA CCGGCGCAGC CATGACAAGC ACTGCCACAA GAAGTACCTG
      ATACACACGC TTCACGTTCT GGCCGCGTCG GTACTGTTTCG TGACGGTGTG CTTTCATGGAC
651  Y V C E   V Q D   R R S   H D K H   C H K   K Y L

2041 TCGGTGCAGG CCCTGGAAGC CCCTCGGCTC ACGCAGAACT TGACCGACCT CCTGGTGAAC
      AGCCACGTCC GGGACCTTCG GGGAGCCGAG TCGTCTTGA ACTGGCTGGA GGACCACTTG
671  S V Q A   L E A   P R L   T Q N L   T D L   L V N

2101 GTGAGCGACT CGCTGGAGAT GCAGTGCTTG GTGGCCGGAG CGCACGCGCC CAGCATCGTG
      CACTCGCTGA GCGACCTCTA CGTCACGAAC CACCGGCCTC GCGTGCGCGG GTCGTAGCAC
691  V S D S   L E M   Q C L   V A G A   H A P   S I V

2161 TGGTACAAAG ACGAGAGGCT GCTGGAGGAA AAGTCTGGAG TCGACTTGGC GGA CTCCAAC
      ACCATGTTTC TGCTCTCCGA CGACCTCCTT TTCAGACCTC AGCTGAACCG CCTGAGGTTG
711  W Y K D   E R L   L E E   K S G V   D L A   D S N

2221 CAGAAGCTGA GCATCCAGCG CGTGC GCGAG GAGGATGCGG GACGCTATCT GTGCAGCGTG
      GTCTTCGACT CGTAGGTCGC GCACGCGCTC CTCCTACGCC CTGCGATAGA CACGTCGCAC
731  Q K L S   I Q R   V R E   E D A G   R Y L   C S V

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FIG. 15D

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2281 TGCAACGCCA AGGGCTGCGT CAACTCCTCC GCCAGCGTGG CCGTGGGAAGG CTCCGAGGAT
    ACGTTGCGGT TCCCGACGCA GTTGAGGAGG CGGTCGCACC GGCACCTTCC GAGGCTCCTA
751 C N A K   G C V   N S S   A S V A   V E G   S E D

2341 AAGGGCAGCA TGGAGATCGT GATCCTTGTC GGTACCGGCG TCATCGCTGT CTTCTTCTGG
    TTCCCGTCGT ACCTCTAGCA CTAGGAACAG CCATGGCCGC AGTAGCGACA GAAGAAGACC
771 K G S M   E I V   I L V   G T G V   I A V   F F W

2401 GTCCTCCTCC TCCTCATCTT CTGTAACATG AGGAGGCCGG CCCACGCAGA CATCAAGACG
    CAGGAGGAGG AGGAGTAGAA GACATTGTAC TCCTCCGGCC GGGTGCGTCT GTAGTTCTGC
791 V L L L   L I F   C N M   R R P A   H A D   I K T

2461 GGCTACCTGT CCATCATCAT GGACCCCGGG GAGGTGCCTC TGGAGGAGCA ATGCGAATAC
    CCGATGGACA GGTAGTAGTA CCTGGGGCCC CTCCACGGAG ACCTCCTCGT TACGCTTATG
811 G Y L S   I I M   D P G   E V P L   E E Q   C E Y

2521 CTGTCTTACG ATGCCAGCCA GTGGGAATTC CCCCAGAGAGC GGCTGCACCT GGGGAGAGTG
    GACAGGATGC TACGGTCGGT CACCCTTAAG GGGGCTCTCG CCGACGTGGA CCCCTCTCAC
831 L S Y D   A S Q   W E F   P R E R   L H L   G R V

2581 CTCGGCTACG GCGCCTTCGG GAAGGTGGTG GAAGCCTCCG CTTTCGGCAT CCACAAGGGC
    GAGCCGATGC CGCGGAAGCC CTTCCACCAC CTTTCGGAGG GAAAGCCGTA GGTGTTCCCG
851 L G Y G   A F G   K V V   E A S A   F G I   H K G

2641 AGCAGCTGTG ACACCGTGGC CGTGAAAATG CTGAAAGAGG GCGCCACGGC CAGCGAGCAC
    TCGTCGACAC TGTGGCACC GCACTTTTAC GACTTTCTCC CGCGGTGCCG GTCGCTCGTG
871 S S C D   T V A   V K M   L K E G   A T A   S E H

2701 CGCGCGCTGA TGTCGGAGCT CAAGATCCTC ATTACATCG GCAACCACCT CAACGTGGTC
    GCGCGCGACT ACAGCCTCGA GTTCTAGGAG TAAGTGTAGC CGTTGGTGGA GTTGCACCAG
891 R A L M   S E L   K I L   I H I G   N H L   N V V

2761 AACCTCCTCG GGGCGTGCAC CAAGCCGCAG GGCCCCCTCA TGGTGATCGT GGAGTTCTGC
    TTGGAGGAGC CCCGCACGTG GTTCGGCGTC CCGGGGGAGT ACCACTAGCA CCTCAAGACG
911 N L L G   A C T   K P Q   G P L M   V I V   E F C

2821 AAGTACGGCA ACCTCTCCAA CTTCTGCGC GCCAAGCGGG ACGCCTTCAG CCCCTGCGCG
    TTCATGCCGT TGGAGAGGTT GAAGGACGCG CGGTTGCCCC TGCGGAAGTC GGGGACGCGC
931 K Y G N   L S N   F L R   A K R D   A F S   P C A

2881 GAGAAGTCTC CCGAGCAGCG CGGACGCTTC CGCGCCATGG TGGAGCTCGC CAGGCTGGAT
    CTCTTCAGAG GGCTCGTCGC GCCTGCGAAG GCGCGGTACC ACCTCGAGCG GTCCGACCTA
951 E K S P   E Q R   G R F   R A M V   E L A   R L D

2941 CGGAGGCGGC CGGGGAGCAG CGACAGGGTC CTCCTCGCGC GGTTCCTCGAA GACCGAGGGC
    GCCTCCGCCG GCCCTCGTC GCTGTCCAG GAGAAGCGCG CCAAGAGCTT CTGGCTCCCG
971 R R R P   G S S   D R V   L F A R   F S K   T E G

3001 GGAGCGAGGC GGGCTTCTCC AGACCAAGAA GCTGAGGACC TGTGGCTGAG CCCGCTGACC
    CCTCGCTCCG CCCGAAGAGG TCTGGTTCTT CGACTCCTGG ACACCGACTC GGGCGACTGG
991 G A R R   A S P   D Q E   A E D L   W L S   P L T

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FIG. 15E

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3061 ATGGAAGATC TTGTCTGCTA CAGCTTCCAG GTGGCCAGAG GGATGGAGTT CCTGGCTTCC
      TACCTTCTAG AACAGACGAT GTCGAAGGTC CACCGGTCTC CCTACCTCAA GGACCGAAGG
1011 M E D L V C Y S F Q V A R G M E F L A S

3121 CGAAAGTGCA TCCACAGAGA CCTGGCTGCT CGGAACATTC TGCTGTCGGA AAGCGACGTG
      GCTTTCACGT AGGTGTCTCT GGACCGACGA GCCTTGTAAG ACGACAGCCT TTCGCTGCAC
1031 R K C I H R D L A A R N I L L S E S D V

3181 GTGAAGATCT GTGACTTTGG CCTTGCCCGG GACATCTACA AAGACCCTGA CTACGTCCGC
      CACTTCTAGA CACTGAAACC GGAACGGGCC CTGTAGATGT TTCTGGGACT GATGCAGGCG
1051 V K I C D F G L A R D I Y K D P D Y V R

3241 AAGGGCAGTG CCCGGCTGCC CCTGAAGTGG ATGGCCCCCTG AAAGCATCTT CGACAAGGTG
      TTCCCGTCAC GGGCCGACGG GGACTTCACC TACCGGGGAC TTTCGTAGAA GCTGTTCAC
1071 K G S A R L P L K W M A P E S I F D K V

3301 TACACCACGC AGAGTGACGT GTGGTCTTTT GGGGTGCTTC TCTGGGAGAT CTCTCTCTG
      ATGTGGTGCG TCTCACTGCA CACCAGGAAA CCCCACGAAG AGACCCTCTA GAAGAGAGAC
1091 Y T T Q S D V W S F G V L L W E I F S L

3361 GGGGCCTCCC CGTACCCTGG GGTGCAGATC AATGAGGAGT TCTGCCAGCG GCTGAGAGAC
      CCCCAGGAGG GCATGGGACC CCACGTCTAG TTACTCCTCA AGACGGTCGC CGACTCTCTG
1111 G A S P Y P G V Q I N E E F C Q R L R D

3421 GGCACAAGGA TGAGGGCCCC GGAGCTGGCC ACTCCCGCCA TACGCCGCAT CATGCTGAAC
      CCGTGTTCCT ACTCCCGGGG CCTCGACCGG TGAGGGCGGT ATGCGGCGTA GTACGACTTG
1131 G T R M R A P E L A T P A I R R I M L N

3481 TGCTGGTCCG GAGACCCCAA GGCGAGACCT GCATTCTCGG AGCTGGTGGA GATCCTGGGG
      ACGACCAGGC CTCTGGGGTT CCGTCTGGA CGTAAGAGCC TCGACCACCT CTAGGACCCC
1151 C W S G D P K A R P A F S E L V E I L G

3541 GACCTGCTCC AGGGCAGGGG CCTGCAAGAG GAAGAGGAGG TCTGCATGGC CCCGCGCAGC
      CTGGACGAGG TCCCCTCCCC GGACGTTCTC CTTCTCCTCC AGACGTACCG GGGCGCGTCC
1171 D L L Q G R G L Q E E E E V C M A P R S

3601 TCTCAGAGCT CAGAAGAGGG CAGCTTCTCG CAGGTGTCCA CCATGGCCCT ACACATCGCC
      AGAGTCTCGA GTCTTCTCCC GTCGAAGAGC GTCCACAGGT GGTACCGGGA TGTGTAGCGG
1191 S Q S S E E G S F S Q V S T M A L H I A

3661 CAGGCTGACG CTGAGGACAG CCCGCCAAGC CTGCAGCGCC ACAGCCTGGC CGCCAGGTAT
      GTCCGACTGC GACTCCTGTC GGGCGGTTCT GACGTCGCGG TGTGCGACCG GCGGTCCATA
1211 Q A D A E D S P P S L Q R H S L A A R Y

3721 TACAACTGGG TGTCTTTTCC CGGGTGCTTG GCCAGAGGGG CTGAGACCCG TGGTTCTCTC
      ATGTTGACCC ACAGGAAAGG GCCCACGGAC CGGTCTCCCC GACTCTGGGC ACCAAGGAGG
1231 Y N W V S F P G C L A R G A E T R G S S

3781 AGGATGAAGA CATTTGAGGA ATTCCCCATG ACCCCAACGA CCTACAAAGG CTCTGTGGAC
      TCCTACTTCT GTAAACTCCT TAAGGGGTAC TGGGGTTGCT GGATGTTTCC GAGACACCTG
1251 R M K T F E E F P M T P T T Y K G S V D

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FIG. 15F

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3841 AACCAGACAG ACAGTGGGAT GGTGCTGGCC TCGGAGGAGT TTGAGCAGAT AGAGAGCAGG
      TTGGTCTGTC TGTCACCCTA CCACGACCGG AGCCTCCTCA AACTCGTCTA TCTCTCGTCC
1271 N   Q   T   D   S   G   M   V   L   A   S   E   E   F   E   Q   I   E   S   R

3901 CATAGACAAG AAAGCGGCTT CAGGTAGCTG AAGCAGAGAG AGAGAAGGCA GCATACGTCA
      GTATCTGTTC TTTCGCCGAA GTCCATCGAC TTCGTCTCTC TCTCTTCCGT CGTATGCAGT
1291 H   R   Q   E   S   G   F   R   O

3961 GCATTTTCTT CTCTGCACTT ATAAGAAAGA TCAAAGACTT TAAGACTTTC GCTATTTCTT
      CGTAAAAGAA GAGACGTGAA TATTTCTTCT AGTTTCTGAA ATTCTGAAAG CGATAAAGAA

4021 CTGCTATCTA CTACAAACTT CAAAGAGGAA CCAGGAGGCC AAGAGGAGCA TGAAAGTGGA
      GACGATAGAT GATGTTTGAA GTTCTCCTT GGTCTCTCCG TTCTCTCTCGT ACTTTCACCT

4081 CAAGGAGTGT GACCACTGAA GCACCACAGG GAGGGGTAG GCCTCCGGAT GACTGCGGGC
      GTTCCTCACA CTGGTGACTT CGTGGTGTCC CTCCCAATC CGGAGGCCTA CTGACGCCCC

4141 AGGCCTGGAT AATATCCAGC CTCCCACAAG AAGCTGGTGG AGCAGAGTGT TCCCTGACTC
      TCCGGACCTA TTATAGGTCG GAGGGTGTTT TTCGACCACC TCGTCTCACA AGGGACTGAG

4201 CTCCAAGGAA AGGGAGACGC CCTTTCATGG TCTGCTGAGT AACAGGTGCC TTCCCAGACA
      GAGGTTCTTT TCCCTCTGCG GGAAAGTACC AGACGACTCA TTGTCCACGG AAGGGTCTGT

4261 CTGGCGTTAC TGCTTGACCA AAGAGCCCTC AAGCGGCCCT TATGCCAGCG TGACAGAGGG
      GACCGCAATG ACGAACTGGT TTCTCGGGAG TTCGCCGGA ATACGGTCGC ACTGTCTCCC

4321 CTCACCTCTT GCCTTCTAGG TCACTTCTCA CAATGTCCCT TCAGCACCTG ACCCTGTGCC
      GAGTGAGAGAA CGGAAGATCC AGTGAAGAGT GTTACAGGGA AGTCGTGGAC TGGGACACGG

4381 CGCCAGTTAT TCCTTGGTAA TATGAGTAAT ACATCAAAGA GTAGT
      GCGGTCAATA AGGAACCAT ATACTCATTA TGTAGTTTCT CATCA

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FIG. 16A

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1 ATGGCTGGGA TTTTCTATTT CGCCCTATTT TCGTGTCTCT TCGGGATTG
  TACCGACCCT AAAAGATAAA GCGGGATAAA AGCACAGAGA AGCCCTAAAC
1 MetAlaGlyI lePheTyrPh eAlaLeuPhe SerCysLeuP heGlyIleCy
  CGACGCTGTC ACAGGTTCCTA GGGTATACCC CGCGAATGAA GTTACCTTAT
  GCTGCGACAG TGTCCAAGGT CCCATATGGG GCGCTTACTT CAATGGAATA
  sAspAlaVal ThrGlySerA rgValTyrPr oAlaAsnGlu ValThrLeuLeu

101 TGGATTCCAG ATCTGTTTCAG GGAGAACTTG GGTGGATAGC AAGCCCTCTG
  ACCTAAGGTC TAGACAAGTC CCTCTTGAAC CCACCTATCG TTCGGGAGAG
  35 AspSerAr gSerValGln GlyGluLeuG lyTrpIleAl aSerProLeu
  GAAGGAGGGT GGGAGGAAGT GAGTATCATG GATGAAAAAA ATACACCAAT
  CTTCCTCCCA CCCTCCTTCA CTCATAGTAC CTACTTTTTT TATGTGGTTA
  GluGlyGlyT rpGluGluVa lSerIleMet AspGluLysA snThrProIle

201 CCGAACCTAC CAAGTGTGCA ATGTGATGGA ACCCAGCCAG AATAACTGGC
  GGCTTGATG GTTCACACGT TACACTACCT TGGGTCGGTC TTATTGACCG
  68 ArgThrTyr GlnValCysA snValMetGl uProSerGln AsnAsnTrpL
  TACGAACTGA TTGGATCACC CGAGAAGGGG CTCAGAGGGT GTATATTGAG
  ATGCTTGACT AACCTAGTGG GCTCTTCCCC GAGTCTCCCA CATATAACTC
  euArgThrAs pTrpIleThr ArgGluGlyA laGlnArgVa lTyrIleGlu

301 ATTAAATTCA CCTTGAGGGA CTGCAATAGT CTTCCGGGCG TCATGGGGAC
  TAATTTAAGT GGAAGTCCCT GACGTTATCA GAAGGCCCGC AGTACCCCTG
101 IleLysPheT hrLeuArgAs pCysAsnSer LeuProGlyV alMetGlyTh
  TTGCAAGGAG ACGTTTAACC TGTACTACTA TGAATCAGAC AACGACAAAG
  AACGTTCCCTC TGCAAATTGG ACATGATGAT ACTTAGTCTG TTGCTGTTTC
  rCysLysGlu ThrPheAsnL euTyrTyrTy rGluSerAsp AsnAspLysGlu

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FIG. 16B

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401 AGCGTTTCAT CAGAGAGAAC CAGTTTGTC A AATTGACAC CATTGCTGCT
    TCGCAAAGTA GTCTCTCTTG GTCAAACAGT TTTAACTGTG GTAACGACGA
135  ArgPheIl eArgGluAsn GlnPheValL ysIleAspTh rIleAlaAla
    GATGAGAGCT TCACCCAAGT GGACATTGGT GACAGAATCA TGAAGCTGAA
    CTA CTCTCGA AGTGGGTTCA CCTGTAACCA CTGTCTTAGT ACTTCGACTT
    AspGluSerP heThrGlnVa lAspIleGly AspArgIleM etLysLeuAsn
501 CACCGAGATC CGGGATGTAG GGCCATTAAG CAAAAAGGGG TTTTACCTGG
    GTGGCTCTAG GCCCTACATC CCGTAATTC GTTTTTCCCC AAAATGGACC
168  ThrGluIle ArgAspValG lyProLeuSe rLysLysGly PheTyrLeuA
    CTTTTCAGGA TGTGGGGGCC TGCATCGCCC TGGTATCAGT CCGTGTGTTC
    GAAAAGTCCT ACACCCCCGG ACGTAGCGGG ACCATAGTCA GGCACACAAG
    laPheGlnAs pValGlyAla CysIleAlaL euValSerVa lArgValPhe
601 TATAAAAAGT GTCCACTCAC AGTCCGCAAT CTGGCCCAGT TTCTGACAC
    ATATTTTTTCA CAGGTGAGTG TCAGGCGTTA GACCGGGTCA AAGGACTGTG
201 TyrLysLysC ysProLeuTh rValArgAsn LeuAlaGlnP heProAspTh
    CATCACAGGG GCTGATACGT CTTCCCTGGT GGAAGTTCGA GGCTCCTGTG
    GTAGTGTCCC CGACTATGCA GAAGGGACCA CCTTCAAGCT CCGAGGACAC
    rIleThrGly AlaAspThrs erSerLeuVa lGluValArg GlySerCysVal
701 TCAACAACCTC AGAAGAGAAA GATGTGCCAA AAATGTACTG TGGGGCAGAT
    AGTTGTTGAG TCTTCTCTTT CTACACGGTT TTTACATGAC ACCCCGTCTA
235  AsnAsnSe rGluGluLys AspValProL ysMetTyrCy sGlyAlaAsp
    GGTGAATGGC TGGTACCCAT TGGCAACTGC CTATGCAACG CTGGGCATGA
    CCACTTACCG ACCATGGGTA ACCGTTGACG GATACGTTGC GACCCGTACT
    GlyGluTrpL euValProIl eGlyAsnCys LeuCysAsnA laGlyHisGlu
801 GGAGCGGAGC GGAGAATGCC AAGCTTGCAA AATTGGATAT TACAAGGCTC
    CCTCGCCTCG CCTCTTACGG TTCGAACGTT TTAACCTATA ATGTTCCGAG
268  GluArgSer GlyGluCysG lnAlaCysLy sIleGlyTyr TyrLysAlaL
    TCTCCACGGA TGCCACCTGT GCCAAGTGCC CACCCACAG CTACTCTGTC
    AGAGGTGCCT ACGGTGGACA CGGTTACGG GTGGGGTGTC GATGAGACAG
    euSerThrAs pAlaThrCys AlaLysCysP roProHisSe rTyrSerVal

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FIG. 16C

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901 TGGGAAGGAG CCACCTCGTG CACCTGTGAC CGAGGCTTTT TCAGAGCTGA
    ACCCTTCCTC GGTGGAGCAC GTGGACACTG GCTCCGAAAA AGTCTCGACT
301 TrpGluGlyA laThrSerCy sThrCysAsp ArgGlyPheP heArgAlaAs
    CAACGATGCT GCCTCTATGC CCTGCACCCG TCCACCATCT GCTCCCTGA
    GTTGCTACGA CGGAGATACG GGACGTGGGC AGGTGGTAGA CGAGGGGACT
    pAsnAspAla AlaSerMetP roCysThrAr gProProSer AlaProLeuAsn
1001 ACTTGATTTC AAATGTCAAC GAGACATCTG TGAACCTGGA ATGGAGTAGC
    TGAACATAAG TTTACAGTTG CTCTGTAGAC ACTTGAACCT TACCTCATCG
335 LeuIleSe rAsnValAsn GluThrSerV alAsnLeuGl uTrpSerSer
    CCTCAGAATA CAGGTGGCCG CCAGGACATT TCCTATAATG TGGTATGCAA
    GGAGTCTTAT GTCCACCGGC GGTCTGTAA AGGATATTAC ACCATACGTT
    ProGlnAsnT hrGlyGlyAr gGlnAspIle SerTyrAsnV alValCysLys
1101 GAAATGTGGA GCTGGTGACC CCAGCAAGTG CCGACCCGTG GGAAGTGGGG
    CTTTACACCT CGACCACTGG GGTCGTTTAC GGCTGGGACA CCTTCACCCC
368 LysCysGly AlaGlyAspP roSerLysCy sArgProCys GlySerGlyV
    TCCACTACAC CCCACAGCAG AATGGCTTGA AGACCACCAA AGGCTCCATC
    AGGTGATGTG GGGTGTGCTC TTACCGAACT TCTGGTGGTT TCCGAGGTAG
    alHisTyrTh rProGlnGln AsnGlyLeuL ysThrThrLy sGlySerIle
1201 ACTGACCTCC TAGCTCATA CATTACACC TTTGAAATCT GGGCTGTGAA
    TGACTGGAGG ATCGAGTATG GTTAATGTGG AAACCTTTAGA CCCGACACTT
401 ThrAspLeuL euAlaHisTh rAsnTyrThr PheGluIleT rpAlaValAs
    TGGAGTGTCC AAATATAACC CTAACCCAGA CCAATCAGTT TCTGTCACTG
    ACCTCACAGG TTTATATTGG GATTGGGTCT GGTTAGTCAA AGACAGTGAC
    nGlyValSer LysTyrAsnP roAsnProAs pGlnSerVal SerValThrVal
1301 TGACCACCAA CCAAGCAGCA CCATCATCCA TTGCTTTGGT CCAGGCTAAA
    ACTGGTGGTT GGTTCGTCGT GGTAGTAGGT AACGAAACCA GGTCCGATTT
435 ThrThrAs nGlnAlaAla ProSerSerI leAlaLeuVa lGlnAlaLys
    GAAGTCACAA GATACAGTGT GGCACCTGGCT TGGCTGGAAC CAGATCGGCC
    CTTCAGTGTT CTATGTCACA CCGTGACCGA ACCGACCTTG GTCTAGCCGG
    GluValThrA rgTyrSerVa lAlaLeuAla TrpLeuGluP roAspArgPro

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FIG. 16D

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1401 CAATGGGGTA ATCCTGGAAT ATGAAGTCAA GTATTATGAG AAGGATCAGA
      GTTACCCCAT TAGGACCTTA TACTTCAGTT CATAATACTC TTCCTAGTCT
468  AsnGlyVal IleLeuGluT yrGluVally sTyrTyrGlu LysAspGlnA
      ATGAGCGAAG CTATCGTATA GTTCGGACAG CTGCCAGGAA CACAGATATC
      TACTCGCTTC GATAGCATAT CAAGCCTGTC GACGGTCCTT GTGTCTATAG
      snGluArgSe rTyrArgIle ValArgThrA laAlaArgAs nThrAspIle
1501 AAAGGCCTGA ACCCTCTCAC TTCCTATGTT TTCCACGTGC GAGCCAGGAC
      TTTCCGGACT TGGGAGAGTG AAGGATACAA AAGGTGCACG CTCGGTCCCTG
501  LysGlyLeuA snProLeuTh rSerTyrVal PheHisVala rgAlaArgTh
      AGCAGCTGGC TATGGAGACT TCAGTGAGCC CTTGGAGGTT ACAACCAACA
      TCGTCGACCG ATACCTCTGA AGTCACTCGG GAACCTCCAA TGTTGGTTGT
      rAlaAlaGly TyrGlyAspP heSerGluPr oLeuGluVal ThrThrAsnThr
1601 CAGTGCCTTC CCGGATCATT GGAGATGGGG CTAACTCCAC AGTCCTTCTG
      GTCACGGAAG GGCCTAGTAA CCTCTACCCC GATTGAGGTG TCAGGAAGAC
535  ValProSe rArgIleIle GlyAspGlyA laAsnSerTh rValLeuLeu
      GTCTCTGTCT CGGGCAGTGT GGTGCTGGTG GTAATTCTCA TTGCAGCTTT
      CAGAGACAGA GCCCGTCACA CCACGACCAC CATTAAAGAGT AACGTCGAAA
      ValSerValS erGlySerVa lValLeuVal ValIleLeuI leAlaAlaPhe
1701 TGTCATCAGC CGGAGACGGA GTAAATACAG TAAAGCCAAA CAAGAAGCGG
      ACAGTAGTCG GCCTCTGCCT CATTTATGTC ATTTCCGTTT GTTCTTCGCC
568  ValIleSer ArgArgArgS erLysTyrSe rLysAlaLys GlnGluAlaA
      ATGAAGAGAA ACATTTGAAT CAAGGTGTAA GAACATATGT GGACCCCTTT
      TACTTCTCTT TGTAAACTTA GTTCCACATT CTTGTATACA CCTGGGGAAA
      spGluGluLy sHisLeuAsn GlnGlyValA rgThrTyrVa lAspProphe

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FIG. 16E

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1801 ACGTACGAAG ATCCCAACCA AGCAGTGC GA GAGTTTGCCA AAGAAATTGA
      TGCATGCTTC TAGGGTTGGT TCGTCACGCT CTCAAACGGT TTCTTTAACT
601  ThrTyrGluA sdProAsnGl nAlaValArq GluPheAlaL ysGluIleAs
      CGCATCCTGC ATTAAGATTG AAAAAGTTAT AGGAGTTGGT GAATTTGGTG
      GCGTAGGACG TAATTCCTAAC TTTTCAATA TCCTCAACCA CTAAACCAC
      pAlaSerCys ileLysIleG luLysValIl eGlyValGly GluPheGlyGlu
1901 AGGTATGCAG TGGGCGTCTC AAAGTGCCTG GCAAGAGAGA GATCTGTGTG
      TCCATACGTC ACCCGCAGAG TTTCACGGAC CGTTCTCTCT CTAGACACAC
635  ValCysSe rGlyArgLeu LysValProG lyLysArgGl uIleCysVal
      GCTATCAAGA CTCTGAAAGC TGGTTATACA GACAAACAGA GGAGAGACTT
      CGATAGTTCT GAGACTTTCG ACCAATATGT CTGTTTGTCT CCTCTCTGAA
      AlaIleLysT hrLeuLysAl aGlyTyrThr AspLysGlnA rgArgAspPhe
2001 CCTGAGTGAG GCCAGCATCA TGGGACAGTT TGACCATCCG AACATCATTC
      GGACTCACTC CGGTCGTAGT ACCCTGTCAA ACTGGTAGGC TTGTAGTAAG
668  LeuSerGlu AlaSerIleM etGlyGlnPh eAspHisPro AsnIleIleH
      ACTTGGAAGG CGTGGTCACT AAATGTAAAC CAGTAATGAT CATAACAGAG
      TGAACCTTCC GCACCAGTGA TTTACATTTG GTCATTACTA GTATTGTCTC
      isLeuGluGl yValValThr LysCysLysP roValMetIl eIleThrGlu
2101 TACATGGAGA ATGGCTCCTT GGATGCATTC CTCAGGAAAA ATGATGGCAG
      ATGTACCTCT TACCGAGGAA CCTACGTAAG GAGTCCTTTT TACTACCGTC
701  TyrMetGluA snGlySerLe uAspAlaPhe LeuArgLysA snAspGlyAr
      ATTTACAGTC ATTCAGCTGG TGGGCATGCT TCGTGGCATT GGGTCTGGGA
      TAAATGTCAG TAAGTCGACC ACCCGTACGA AGCACCCTAA CCCAGACCCT
      gPheThrVal ileGlnLeuV alGlyMetLe uArgGlyIle GlySerGlyMet
2201 TGAAGTATTT ATCTGATATG AGCTATGTGC ATCGTGATCT GGCCGCACGG
      ACTTCATAAA TAGACTATAC TCGATACACG TAGCACTAGA CCGGCGTGCC
735  LysTyrLe uSerAspMet SerTyrValH isArgAspLe uAlaAlaArg
      AACATCCTGG TGAACAGCAA CTTGGTCTGC AAAGTGTCTG ATTTTGGCAT
      TTGTAGGACC ACTTGTCGTT GAACCAGACG TTTCACAGAC TAAAACCGTA
      AsnIleLeuV alAsnSerAs nLeuValCys LysValSerA spPheGlyMet

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FIG. 16F

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2301 GTCCCGAGTG CTTGAGGATG ATCCGGAAGC AGCTTACACC ACCAGGGGTG
      CAGGGCTCAC GAACTCCTAC TAGGCCTTCG TCGAATGTGG TGGTCCCCAC
768  SerArgVal LeuGluAspA spProGluAl aAlaTyrThr ThrArgGlyG
      GCAAGATTCC TATCCGGTGG ACTGCGCCAG AAGCAATTGC CTATCGTAAA
      CGTTCTAAGG ATAGGCCACC TGACGCGGTC TTCGTTAACG GATAGCATT
      lyLysIlePr oIleArgTrp ThrAlaProG luAlaIleAl aTyrArgLys
2401 TTCACATCAG CAAGTGATGT ATGGAGCTAT GGAATCGTTA TGTGGGAAGT
      AAGTGTAGTC GTTCACTACA TACCTCGATA CCTTAGCAAT ACACCCCTCA
801  PheThrSerA laSerAspVa lTrpSerTyr GlyIleValM etTrpGluVa
      GATGTCGTAC GGGGAGAGGC CCTATTGGGA TATGTCCAAT CAAGATGTGA
      CTACAGCATG CCCCTCTCCG GGATAACCCT ATACAGGTTA GTTCTACACT
      lMetSerTyr GlyGluArgP roTyrTrpAs pMetSerAsn GlnAspValIle
2501 TTAAAGCCAT TGAGGAAGGC TATCGGTTAC CCCCTCCAAT GGACTGCCCC
      AATTTTCGGTA ACTCCTTCCG ATAGCCAATG GGGGAGGTTA CCTGACGGGG
835  LysAlaIl eGluGluGly TyrArgLeuP roProProMe tAspCysPro
      ATTGCGCTCC ACCAGCTGAT GCTAGACTGC TGGCAGAAGG AGAGGAGCGA
      TAACGCGAGG TGGTCGACTA CGATCTGACG ACCGTCTTCC TCTCCTCGCT
      IleAlaLeuH isGlnLeuMe tLeuAspCys TrpGlnLysG luArgSerAsp
2601 CAGGCCTAAA TTTGGGCAGA TTGTCAACAT GTTGGACAAA CTCATCCGCA
      GTCCGGATTT AAACCCGTCT AACAGTTGTA CAACCTGTTT GAGTAGGCGT
868  ArgProLys PheGlyGlnI leValAsnMe tLeuAspLys LeuIleArgA
      ACCCCAACAG CTTGAAGAGG ACAGGGACGG AGAGCTCCAG ACCTAACACT
      TGGGGTTGTC GAACTTCTCC TGTCCTGCC TCTCGAGGTC TGGATTGTGA
      snProAsnSe rLeuLysArg ThrGlyThrG luSerSerAr gProAsnThr

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FIG. 16G

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2701 GCCTTGTTGG ATCCAAGCTC CCCTGAATTC TCTGCTGTGG TATCAGTGGG
      CGGAACAACC TAGGTTCGAG GGGACTTAAG AGACGACACC ATAGTCACCC
901  AlaLeuLeuA spProSerSe rProGluPhe SerAlaValV alSerValGl
      CGATTGGCTC CAGGCCATTA AAATGGACCG GTATAAGGAT AACTTCACAG
      GCTAACCGAG GTCCGGTAAT TTTACCTGGC CATATTCCTA TTGAAGTGTC
      yAspTrpLeu GlnAlaIleL ysMetAspAr gTyrLysAsp AsnPheThrAla
2801 CTGCTGGTTA TACCACACTA GAGGCTGTGG TGCACGTGAA CCAGGAGGAC
      GACGACCAAT ATGGTGTGAT CTCCGACACC ACGTGCACTT GGTCTCTCTG
935   AlaGlyTy rThrThrLeu GluAlaValV alHisValAs nGlnGluAsp
      CTGGCAAGAA TTGGTATCAC AGCCATCACA CACCAGAATA AGATTTTGTAG
      GACCGTTCTT AACCATAGTG TCGGTAGTGT GTGGTCTTAT TCTAAAACTC
      LeuAlaArgI leGlyIleTh rAlaIleThr HisGlnAsnL ysIleLeuSer
2901 CAGTGTCCAG GCAATGCGAA CCCAAATGCA GCAGATGCAC GGCAGAATGG
      GTCACAGGTC CGTTACGCTT GGGTTTACGT CGTCTACGTG CCGTCTTACC
968   SerValGln AlaMetArgT hrGlnMetGl nGlnMetHis GlyArgMetV
      TTCCCGTCTG AGCCAGTACT GAATAAACTC AAAACTCTTG AAATTAGTTT
      AAGGGCAGAC TCGGTCATGA CTTATTTGAG TTTTGAGAAC TTTAATCAAA
      alProValOp *AlaSerThr GluOc*ThrG lnAsnSerOp *AsnAm*Phe
3001 ACCTCATCCA TGCACTTTAA TTGAAGAACT GCACTTTTTT TACTTCGTCT
      TGGAGTAGGT ACGTGAAATT AACTTCTTGA CGTGAAAAAA ATGAAGCAGA
1001 ThrSerSerM etHisPheAs nOp*ArgThr AlaLeuPheL euLeuArgLe
      TCGCCCTCTG AAATTAAAGA AATGAAAAAA AAAAAACAAT ATCTGCAGCG
      AGCGGGAGAC TTTAATTTCT TTACTTTTTT TTTTTTGTTA TAGACGTCGC
      uArgProLeu LysLeuLysL ysOp*LysLy sLysAsnAsn IleCysSerVal

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FIG. 16H

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3101 TTGCTTGGTG CACAGATTGC TGAAACTGTG GGGCTTACAG AAATGACTGC
AACGAACCAC GTGTCTAACG ACTTTGACAC CCCGAATGTC TTTACTGACG
1035 AlaTrpCv sThrAspCvs Op*AsnCvsG lvAlaTvrAr qAsnAspCvs
CGGTCATTTG AATGAGACCT GGAACAAATC GTTTCCTCAGA AGTACTTTTC
GCCAGTAAAC TTTACTCTGGA CCTTGTTTTAG CAAAGAGTCT TCATGAAAAG
ArgSerPheG luOp*AspLe uGluGlnIle ValSerGlnL vsTyrPheSer
3201 TGTTCATCAC CAGTCTGTAA AATACATGTA CCTATAGAAA TAGAACACTG
ACAAGTAGTG GTCAGACATT TTATGTACAT GGATATCTTT ATCTTGTGAC
1068 ValHisHis GlnSerValL ysTyrMetTy rLeuAm*Lys Am*AsnThrA
CCTCTGAGTT TTGATGCTGT ATTTGCTGCC AGACACTGAG CTTCTGAGAC
GGAGACTCAA AACTACGACA TAAACGACGG TCTGTGACTC GAAGACTCTG
laSerGluPh eOp*CysCys IleCysCysG lnThrLeuSe rPheOp*Asp
3301 ATCCCTGATT CTCTCTCCAT TTGGAATTAC AACGGTCGAC GAGCTCGA
TAGGGACTAA GAGAGAGGTA AACCTTAATG TTGCCAGCTG CTCGAGCT
1101 IleProAspS erLeuSerIl eTrpAsnTyr AsnGlyArgA rgAlaArg

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INTERNATIONAL SEARCH REPORT

Intern: 1 Application No
PCT/US 95/04228

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/12 C07K16/28 C07K19/00 C12N5/10 C12N15/85
A61K39/395

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C12N C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,93 15201 (NEW ENGLAND DEACONESS HOSPITAL) 5 August 1993 see page 13, line 1-13 see figures see claims ---	1-15
A	THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 267, no. 36, 25 December 1992 BALTIMORE, MD, USA, pages 26166-26171, M. MARK ET AL. 'Expression and characterization of hepatocyte growth factor receptor-IgG fusion proteins.' see the whole document --- -/--	8-15

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

19 July 1995

Date of mailing of the international search report

01.08.95

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INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JOURNAL OF CELLULAR PHYSIOLOGY, vol. 158, no. 3, March 1994 NEW YORK, NY, USA, pages 545-554, L. ASHMAN ET AL. 'Epitope mapping and functional studies with three monoclonal antibodies to the c-kit receptor tyrosine kinase, YB5.B8, 17F11, and SR-1.' see abstract ---	1-7
A	GROWTH REGULATION, vol. 1, no. 2, June 1991 EDINBURGH, GB, pages 72-82, J. SARUP ET AL. 'Characterization of an anti-p185HER2 monoclonal antibody that stimulates receptor function and inhibits tumor cell growth.' see abstract ---	1-7
A	CANCER RESEARCH, vol. 52, no. 3, 1 February 1992 PHILADELPHIA, PA, USA, pages 746-748, O. APRELIKOVA ET AL. 'FLT4, a novel class III receptor tyrosine kinase in chromosome 5q33-qter.' see abstract see figure 1 ---	8-15
P,X	PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE USA, vol. 92, no. 6, 14 March 1995 WASHINGTON, DC, USA, pages 1866-1870, B. BENNETT ET AL. 'Molecular cloning of a ligand for the EPH-related receptor protein-tyrosine kinase Htk.' see the whole document ---	1-15
P,X	THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 269, no. 19, 13 May 1994 BALTIMORE, MD, USA, pages 14211-14218, B. BENNETT ET AL. 'Cloning and characterization of HTK, a novel transmembrane tyrosine kinase of the EPH subfamily.' see the whole document ---	1,3,7-9, 11-15

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INTERNATIONAL SEARCH REPORT

Internat'l Application No

PCT/US 95/04228

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	<p>BLOOD, vol. 84, no. 8, 15 October 1994 NEW YORK, NY, USA, pages 2422-2430, F. ZEIGLER ET AL. 'Cellular and molecular characterization of the role of the FLK-2/FLT-3 receptor tyrosine kinase in hematopoietic stem cells.' see the whole document -----</p>	1-7

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 95/04228

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9315201	05-08-93	AU-B- 3482493	01-09-93
		CA-A- 2128722	05-08-93
		EP-A- 0624192	17-11-94
		JP-T- 7504813	01-06-95
